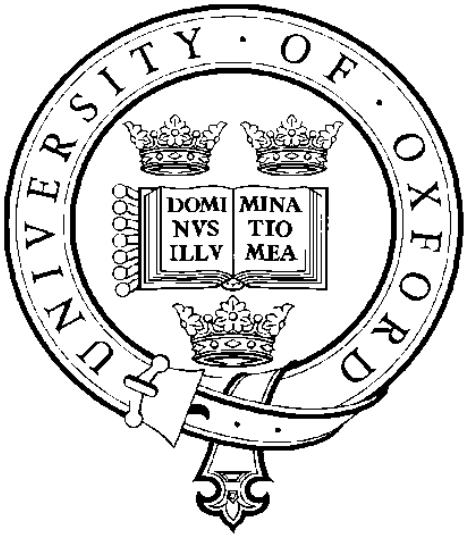
Compulsivity in Anorexia Nervosa.

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This thesis is submitted for the degree of Doctor of Philosophy

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Abstract

Anorexia Nervosa (AN) is a psychiatric disorder characterised by persistent self-starvation, which has high mortality rates, and low rates of recovery. In conjunction with a lack of effective treatments, the serious nature of the disorder emphasises the need for research investigating the underlying processes contributing the persistence of the disorder, and the identification of novel avenues for treatment development.

In individuals with AN, dietary restriction often takes on a driven and compulsive quality, with increasing suggestion of parallels with other disorders featuring compulsive behaviour, such as Obsessive-Compulsive Disorder (OCD) and substance dependence. The commonalities and comorbidities in compulsive behaviours across a range of disorders have been highlighted by Robbins et al (2012), who propose a transdiagnostic approach to compulsivity, arguing that this behavioural construct has cross-diagnostic significance. Conceptualising compulsivity in this way may aid in the development of novel research avenues investigating the learning processes and neurobiological mechanisms underpinning this behaviour. In light of this, the aim of this thesis was to investigate the compulsive nature of behaviour in AN, and the behavioural and neural underpinnings of this behaviour guided by research carried out in other compulsive disorders.

Chapter 1 reviews models of the neural and behavioural underpinnings of compulsive behaviour, and discusses these in relation to compulsive behaviour in AN. Chapter 2 presents qualitative data supporting parallels between the subjective experience of compulsive behaviour in AN and substance use disorders (SUDs). These parallels are further examined in Chapter 3, in which two novel measures of compulsive weight-loss behaviour were developed and validated by adapting a questionnaire assessing addictive behaviour. Chapter 4 presents data suggesting that these parallels in behaviour do not reflect a common tendency to develop habits in learning, as found in substance dependence and OCD. The electrophysiological data presented in Chapter 5 was unable to provide evidence that AN may be underpinned by dysfunction of the neurocircuitry seen in other compulsive disorders. Whilst these studies support suggestion of parallels with substance dependence, at least at the level of self-report, the hypothesised parallels in the underlying behavioural and neural mechanisms were not found.

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Declarations

I declare that the work presented in this thesis is my own and has not been submitted for any other degrees in this or in any other university or institute of learning.

Some of the work described in this thesis has previously been published, or is currently in submission.

Chapter 1

Godier, L.R., and Park, R.J. (2014). Compulsivity in anorexia nervosa: a transdiagnostic concept. *Frontiers in Psychology*,5, 778.

Park, R.J., Godier, L.R., and Cowdrey, F.A. (2014). Hungry for reward: How can neuroscience inform the development of treatment for Anorexia Nervosa? *Behaviour Research and Therapy*, *62*, 47-59.

Chapter 2

Godier, L.R., and Park, R.J. (under review). Does Anorexia Nervosa resemble an addiction? A qualitative investigation. *Frontiers in Psychology, 6,* 1608.

Chapter 3

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Chapter 4

Godier, L.R., de Wit, S., Pinto, A., Steinglass, J.E., Greene, A.L., Scaife, J.C., Gillan, C.M., Walsh, B.T., Simpson, H.B., and Park, R.J. (under review). An investigation of habit learning in Anorexia Nervosa. *Psychiatry Research.*

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List of Abbreviations

5-HT	5-hydroxytryptamine
AAQ	Acceptance and Action Questionnaire
ABA	Activity Based Anorexia
ACC	Anterior Cingulate Cortex
AN	Anorexia Nervosa
ANOVA	Analysis of Variance
BDI	Beck Depression Inventory
BED	Binge eating disorder
BIS	Barratt Impulsiveness Scale
BMI	Body mass index
BN	Bulimia Nervosa
CBT	Cognitive behavioural therapy
CES	Compulsive Exercise Scale
CET	Compulsive Exercise Test
CIA	Clinical Impairment Assessment
CS	Conditioned Stimulus
CSF	Cerebrospinal Fluid
DA	Dopamine
DBS	Deep Brain Stimulation
DMN	Default mode network
DSM-IV	Diagnostic and Statistical Manual (Edition IV)
DSM-V	Diagnostic and Statistical Manual (Edition V)
DTI	Diffusion Tensor Imaging
ED	Eating disorder
EDE	Eating Disorder Examination
EDE-Q	Eating Disorder Examination Questionnaire
EEG	Electroencephalography

FAA	Food Anticipation Activity
FMRI	Functional magnetic resonance imaging
FSL	FMRIB Software Library
GABA	Gamma-amino butyric acid
GAD	Generalised Anxiety Disorder Assessment
GLM	General Linear Model
HC	Healthy control
HVA	Homovanillic acid
ICA	Independent component analysis
ICD-10	International Classification of Disease (10th Edition)
IPT	Interpersonal psychotherapy
IQ	Intelligence Quotient
LDQ	Leeds Dependence Questionnaire
MEG	Magnetoencephalography
MDD	Major Depressive Disorder
MNI	Montreal Neurological Institute
NAc	Nucleus Accumbens
NART	National Adult Reading Test Revised
NICE	National Institute of Clinical Excellence
NIMH	National Institute of Mental Health
NOS	Eating disorder not otherwise specified
NRES	National Research Ethics Service
OCD	Obsessive compulsive disorder
OCI-r	Obsessive-Compulsive Inventory - revised
OCPD	Obsessive-Compulsive Personality Disorder
OFC	Orbitofrontal Cortex
ORLA	Oxford Research-Interest List for Anorexia Nervosa
OSL	Oxford Software Library
PCA	Principal Components Analysis

PFC	Prefrontal Cortex
PHQ	Patient Health Questionnaire
PTSD	Post-Traumatic Stress Disorder
RDoC	Research Doman Criteria
RRS-ED	Ruminative Response Scale for Eating Disorders
RSN	Resting state network
rTMS	Repetitive transcranial magnetic stimulation
SCID	Structured Clinical Interview for DSM-IV
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
SS	Self-Starvation Scale
SNRI	Selective Noradrenaline Reuptake Inhibitors
SPM	Statistical Parametric Mapping
SPSRQ	Sensitivity to Punishment and Sensitivity to Reward Questionnaire
SSRI	Selective Serotonin Reuptake Inhibitors
STAI	State Trait Anxiety Scale
SUD	Substance Use Disorder
TA	Thamatic Analysis
VAS	Visual analogue scale
VS	Ventral Striatum
YBC-EDs-SRQ	Yale Brown Cornell Eating Disorder Scale Self-Report Questionnaire
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale
YFAS	Yale Food Addiction Scale

Preface

The aim of this thesis was to explore a transdiagnostic perspective on compulsivity in relation to behaviour in Anorexia Nervosa (AN), in order to help delineate behavioural and neural underpinnings of persistent weight loss behaviour in AN. A number of different methodologies were used to investigate this aim, including participants both currently ill and recovered from AN and healthy controls. The subjective experience of compulsivity AN was investigated and compared to substance dependence using qualitative techniques in Chapter 2, complemented by the development of measures to capture compulsive behaviour in Chapter 3. The behavioural and neural underpinnings of compulsive behaviour were then investigated in Chapters 4 and 5.

Chapter 1

Part 1

In the first part of the introduction definitions for AN and compulsivity are provided, and diagnosis, prevalence, comorbidity and treatment recommendations are outlined briefly. This section emphasises the need for translational research for novel treatment development in AN, for which effective treatment strategies are lacking, and provides a rationale for investigating transdiagnostic aspects of behaviour in AN.

Part 2

This section explores the idea of compulsivity as a transdiagnostic concept, seen in various manifestations across compulsive disorders including AN. The neural and behavioural underpinnings of compulsive behaviour are reviewed and discussed in relation to the possible role they may play in the persistence of compulsive weight loss behaviour in AN.

Part 3

The final part of the introduction focuses on issues of research design in AN, taking into account literature reviewed in parts 1 and 2. Methodological issues relating to comorbidities and subtypes, medication status and malnutrition are considered.

Chapter 2

The validity of suggested similarities between AN and substance dependence was investigated with a qualitative analysis in which individuals with a current diagnosis of AN were asked to reflect on their experience of compulsivity in AN. The results of this study suggested that individuals with AN view the compulsive nature of their behaviour as central to the maintenance of their disorder, and as a significant barrier to recovery. The themes that emerged from this analysis closely paralleled the DSM-V criteria for Substance Use Disorders, supporting suggestion in Chapter 1 of parallels between the disorders. These results emphasised the need for further research to explore the behavioural and neural underpinnings of compulsivity in AN, and its transdiagnostic significance.

Chapter 3

The results of the study reported in Chapter 2 suggested that the subjective experience of compulsive weight loss behaviour in AN can be considered comparable to the characteristic behaviours inherent in substance dependence. To further investigate behavioural parallels between AN and substance dependence, two novel measures of compulsive weight loss behaviour were developed by adapting the criteria for addiction to capture compulsive exercise and restriction in AN. These measures demonstrated good reliability and validity in both a community sample, and a sample of individuals with

experience of AN (current and past). The results emphasised the utility of using the criteria of dependence in capturing compulsive weight loss behaviour, and support the transdiagnostic relevance of compulsive behaviour, on which disorder-specific themes may be superimposed.

Chapter 4

The results of Chapters 2 and 3 led to the question of whether the observed parallels in the compulsive nature of behaviour are reflected in the underlying mechanisms driving this behaviour in AN and other compulsive disorders. Chapter 1 introduced the habit theory of OCD and substance dependence, in which aberrant habit formation is suggested to underpin the persistence of maladaptive behaviour in these disorders. This chapter investigated the suggestion that habit formation may also be aberrant in AN using two experimental paradigms previously in OCD and substance dependence to assess the persistence of habits. Both currently ill and recovered individuals in this study showed no deficits in performance compared to controls on either of these tasks. Thus no evidence was found that individuals with AN have a generalised vulnerability to develop habits in learning as has been reported in other compulsive disorders. The possibility of a vulnerability to develop disorder-related habits, rather than general habits, as a result of aberrant disorder-related reward in AN is discussed.

Chapter 5

In Chapter 4 it was proposed that whilst there may be no pervasive tendency to rely on habits in AN, compulsive weight-loss behaviour may be the result of increased goal-directed pursuit of disorder-related reward. This may be reflected in alterations in neural systems supporting compulsive behaviour. This chapter aimed to investigate the possible

neural underpinnings of AN by looking at the activity of resting state neural networks in individuals with experience of AN (current and past), and how this might related to measures of compulsivity such as those developed in Chapter 3. Whilst the majority of research looking at resting state neural networks has used fMRI, this study used MEG, which has superior temporal resolution. However, no alterations in the temporal coherence of resting state neural networks were found in individuals with experience of AN (current or past) compared to healthy controls. As such, it was not possible to investigate an association between RSN dysfunction and measures of compulsive behaviour in AN. Methodological limitations and low statistical power that may have contributed to this null result are discussed.

Chapter 6

Chapter 6 summarises the research findings reported in this thesis. Based on the findings of Chapters 2-4 and the literature reviewed in Chapter 1, a model is proposed for the development of disorder-specific habitual behaviour in AN. This model suggests that aberrant disorder-related reward, in conjunction with the physiological consequences of starvation in AN, lead to weight-loss behaviour becoming habitual over time. Theoretical and clinical implications of this research are discussed, and limitations are considered. Finally, future directions for research are suggested.

1. Compulsivity in Anorexia Nervosa

1.1 Overview of Introduction Part 1: Diagnosis, comorbidity, and treatment in Anorexia Nervosa

This chapter provides an overview of the literature relating to Anorexia Nervosa (AN) and the compulsive nature of weight-loss behaviour in this disorder. The chapter is divided into three sections. Part 1 provides working definitions of AN and compulsivity. Diagnosis, prevalence, comorbidity and treatments recommendations for AN are then briefly reviewed. The reviewed literature emphasises the serious nature of the disorder, and need for translational research to develop novel avenues for treatment development. Part 2 of this chapter reviews the behavioural and neurobiological correlates of compulsivity in AN and across disorders, and provides a rationale for investigating the transdiagnostic nature of compulsive behaviour in AN. Part 3 discusses considerations for research design in AN in light of the literature discussed in Part 1 and 2.

1.2 Working definitions

Anorexia Nervosa (AN) is defined according to the Diagnostic and Statistical Manual for Mental Disorders (DSM-V) criteria (American Psychiatric Association, 2013), as described in Section 1.3.1, or the International Classification of Disease (ICD-10) (World Health Organisation, 1992).

Compulsivity can be defined as a trait leading to behaviour that is inappropriate to the situation, persists despite having no relationship with any overall goal, and results in undesirable consequences (Dalley, Everitt, & Robbins, 2011). For the purpose of this thesis compulsive behaviour will be defined as: persistent behaviour, experienced as being outside of the individual's control, which continues despite pervasive adverse physical or psychological consequences.

1.3 Diagnostic classification of Anorexia Nervosa

AN is a severely debilitating psychiatric disorder characterised by relentless self-starvation with dramatic physiological and psychological effects. It is associated with low rates of recovery (Berkman, Lohr, & Bulik, 2007), and has the highest mortality rate of any psychiatric disorder (Arcelus, Mitchell, Wales, & Nielsen, 2011). Individuals with AN place extreme over-importance on the control of weight and shape, which becomes central to their self-evaluation, and often have disturbed body image perception (Fairburn, Cooper, & Shafran, 2003). These distorted beliefs and perceptions are accompanied by a lack of concern over extreme emaciation, a perpetual drive for thinness, and continuous lowering of weight goals (Barbarich-Marsteller, Foltin, & Walsh, 2011). The diagnostic criteria for AN (See Section 1.3.1) encompasses these behaviours and beliefs.

1.3.1 DSM-V diagnostic criteria for Anorexia Nervosa

To be diagnosed as having AN a person must display:

A. *Persistent restriction of energy intake leading to significantly low body weight (in the context of what is minimally expected for age, sex, developmental trajectory, and physical health).*

B. *Either an intense fear of gaining weight or of becoming fat, or persistent behaviour that interferes with weight gain (even though significantly low weight).*

C. *Disturbance in the way one's body weight or shape is experienced, undue influence of body shape and weight on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.*

Subtypes:

Restricting Type – During the last three months, the person has not engaged in recurrent episodes of binge eating or purging behaviour (i.e. self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

Binge/Purge Type – During the last three months, the person has engaged in recurrent episodes of binge eating or purging behaviour (i.e. self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

1.3.2 Differences in diagnosis between DSM-IV and DSM-V

The previous DSM-IV scheme for EDs recognised two disorders, AN and Bulimia Nervosa (BN), and a residual diagnosis of 'Not Otherwise Specified' (NOS) given to those who do not meet the full criteria for AN or BN (American Psychiatric Association, 2000). This scheme was criticised due to high levels of NOS diagnoses, reported to have made up

half of ED diagnoses (Fairburn et al., 2007). In addition, individuals with a NOS diagnosis showed many of the clinical features of AN or BN, in different combinations (Fairburn et al., 2007). As a result of this, the DSM-V criteria for AN was amended in order to be more inclusive of those with a residual NOS diagnosis (Smink, van Hoeken, Oldehinkel, & Hoek, 2014). The previous amenorrhea requirement was excluded, as this was already waived in a number of situations (e.g. in males, females taking oral contraceptive medication, and postmenopausal women), and the symptomology of those without amenorrhea closely resembled those who met this criteria. The wording of criterion A was amended from the previous requirement of 85% of expected body weight to a more inclusive 'significantly low body weight', and advice regarding how to judge this is included. Criterion B was also expanded to include those who do not report a fear of weight gain, but still present with behaviour that interferes with weight gain. Studies comparing the DSM-IV and DSM-V criteria for EDs have shown that the new scheme is successful in reducing diagnoses of residual diagnoses (Birgegard, Norring, & Clinton, 2012; Keel, Brown, Holm-Denoma, & Bodell, 2011; Smink et al., 2014; Walsh & Sysko, 2009) .

1.3.3. How does AN differ from other eating disorders?

Whilst all EDs are defined by their extremes of food consumption, individual diagnoses differ in their characteristic behaviours, carried out in the pursuit of weight loss. The ability to maintain food restriction despite emaciation in AN is in stark contrast to the cycle of under and overeating seen in BN, which is also relevant for the binge/purge subtype of AN and BED. These differences may be underpinned by opposing extremes of inhibitory self control in these disorders. Indeed, individuals with AN, particularly the restrictive subtype, tend to be over-controlled and concerned with future consequences, whereas individuals with BN show poor impulse control and reduced fear of future

consequences (Kaye, Fudge, & Paulus, 2009; Wu, Hartmann, Skunde, Herzog, & Friederich, 2013). Extreme self control is reflected in the increased tendency to delay immediate monetary reward in AN, in favour of a larger future reward (Steinglass, Figner, et al., 2012),

Furthermore, neurobiological alterations have been reported in the balance between reward and inhibition in AN and BN (Wierenga et al., 2014). Neuroimaging studies in AN have reported a reduced response to both food images (Gizewski et al., 2010; Holsen et al., 2012; Uher et al., 2003) , and receipt of food in brain reward circuitry (Vocks, Herpertz, Rosenberger, Senf, & Gizewski, 2011; Wagner et al., 2008). In conjunction with enhanced activity in regions associated with inhibitory cognitive control (Wierenga et al., 2015; Zastrow et al., 2009), this suggests restrictive eating in AN may result from excessive cognitive control processes and decreased valuation of food reward (Wierenga et al., 2014). In contrast to this, individuals with BN show an increased response to food cues (Brooks, O′Daly, et al., 2011; Weygandt, Schaefer, Schienle, & Haynes, 2012) and receipt of food in reward circuitry (Oberndorfer et al., 2013; Radeloff et al., 2014), as well as failure to appropriately engage frontostriatal circuits, suggestive of reduced inhibition (Marsh et al., 2011; Marsh et al., 2009). This increased response to reward and dysregulated inhibitory control may underpin the cycle of binge/purge behaviour seen in BN and binge/purge AN, in which dietary control cannot be maintained (Wierenga et al., 2014).

1. 4 Prevalence and Co-morbidities

The majority of the literature pertaining to the prevalence of AN in the general population has used the DSM-IV criteria, and lifetime prevalence reported using this criteria have ranged from 0.6-2.0% (Favaro, Ferrara, & Santonastaso, 2003; Kjelsas, Bjornstrom, & Gotestam, 2004; Lewinsohn, Striegel-Moore, & Seeley, 2000; Stice, Marti, Shaw, & Jaconis, 2009). However, a recent study using the new DSM-V criteria reported a lifetime prevalence of 0.8% (Stice, Marti, & Rohde, 2013), a slight increase compared to 0.6% reported previously using the DSM-IV criteria in the same sample (Stice et al., 2009). This increase is likely due to the more inclusive nature of the DSM-V criteria.

Comorbidity is high in AN, with one study reporting that 56.2% of individuals with AN met the criteria for at least one other DSM-IV disorder (Hudson, Hiripi, Pope Jr, & Kessler, 2007). AN is most often associated with comorbid diagnoses of depression and anxiety disorders (Aspen et al., 2014), and the presence of EDs in the general population is more frequent in those with a mood or anxiety disorder (Zaider, Johnson, & Cockell, 2000).

A review the literature concerning the comorbidity of mood disorders in EDs, found a lifetime prevalence of major depressive disorder (MDD) in restrictive AN of between 9.5-64.7% and 50-71.3% in binge/purge AN (Godart et al., 2007). Malnutrition is associated with higher depressive symptoms (Keys, Brozek, Henschel, Mickelsen, & Taylor, 1950; Pollice, Kaye, Greeno, & Weltzin, 1997), which has been suggested to inflate comorbidity estimates. However, elevated depression is also found in recovered AN (Holtkamp, Muller, Heussen, Remschmidt, & Herpertz-Dahlmann, 2005), suggesting this may be a trait rather than state-related factor. Comorbid mood disorders are associated

with a worse outcome in AN (Keski-Rahkonen et al., 2014), and higher risk of suicide (Franko et al., 2004).

The presence of anxiety disorders, such as obsessive-compulsive disorder (OCD), social and specific phobias, generalised anxiety disorder (GAD), and post-traumatic stress disorder (PTSD), are common in AN (Godart, Flament, Perdereau, & Jeammet, 2002; Kaye, Bulik, Thornton, Barbarich, & Masters, 2004; Swinbourne et al., 2012). Of note is the observation that starvation may induce obsessional and anxious symptoms in otherwise healthy individuals (Keys et al., 1950), suggesting that anxiety-related symptoms may arise as a result of malnutrition. However, these symptoms are also been found to persist to some degree after weight restoration (Pollice et al., 1997). Moreover, anxiety disorders and obsessive-compulsive symptoms are found to predate the onset of AN, as well as persist following recovery, suggesting an anxious and obsessional temperament may be a trait factor in AN (Anderluh, Tchanturia, Rabe-Hesketh, & Treasure, 2003; Holtkamp et al., 2005; Kaye et al., 2004; Swinbourne et al., 2012). Comorbid OCD is associated with earlier onset and longer duration of AN (Milos, Spindler, Ruggiero, Klaghofer, & Schnyder, 2002), although the literature regarding the outcomes associated with anxiety disorders in general in AN is inconsistent (Hughes, 2012).

EDs as a whole are reported to have increased comorbidity with substance use disorders (SUDs), although estimates of comorbidity vary greatly. The US National Centre on Addiction and Substance Abuse found that up to 50% of individuals with an eating disorder abuse substances compared with 9% of the general population, and up to 35% of individuals with substance abuse have an eating disorder compared with 3% of the general population (Baker et al., 2013; CASA, 2003). A review of the literature suggests SUDS are less common in those with AN, particularly in the restrictive subtype, with a lifetime prevalence of 2-10% in AN (Holderness, 1994). However, a more recent study reported a

much higher lifetime comorbidity of 27% in AN (Hudson et al., 2007). Severity of caloric restriction has been found to be predictive of substance use, independent of the diagnostic category, suggesting a possible relationship between restrictive behaviour and substance use (Wiederman & Pryor, 1996). Substance use has also been associated with higher risk of suicide in AN (Franko et al., 2004).

SUDs are reported to be more common in individuals whose EDs feature bingeing. In BN estimates of prevalence range between 8-40% (Holderness, Brooks-Gunn, & Warren, 1994), and 24.8% of individuals with BED report a lifetime SUD (Grilo, White, & Masheb, 2009). Furthermore, adapting the criteria for substance dependence has been used to capture aspects of 'food addiction' (Gearhardt, Corbin, & Brownell, 2009). The concept of food addiction is proposed to be characterised by similar behaviour to that seen in substance dependence (i.e diminished control during consumption, and diminished ability to reduce the quantity/frequency of intake) (Gearhardt, White, & Potenza, 2011). Proponents suggest there may be a specific relationship between the binge-purge cycle of behaviour, which may itself take on an addictive quality, and substance addiction (Gearhardt et al., 2009; O'Brien & Vincent, 2003). However, this model has been criticised by those who suggest there is currently little evidence to support these parallels to substance addiction at a neuroscientific level (Ziauddeen & Fletcher, 2013).

1.5 Treatment recommendations for Anorexia Nervosa

There is a huge lack of effective treatments for AN in adults, particularly once established, and up to half do not recover (Steinhausen, 2002), going on to develop Severe Enduring AN (SEAN), defined as having AN for over 7 years (Touyz et al., 2013). Reviews of the literature indicate that the current evidence base does not lend support to any one particular psychotherapeutic treatment method in adult AN (Brown & Keel, 2012; Bulik, Berkman, Brownley, Sedway, & Lohr, 2007), whilst family based therapy may be a superior treatment in adolescent AN (Brown & Keel, 2012). In a study comparing different psychotherapies in the treatment of AN, McIntosh et al (2005) illustrate a lack of evidence for the superiority of one treatment type. They compared cognitive behavioural therapy (CBT), and interpersonal psychotherapy (IPT), with a control treatment combining clinical management and supportive psychotherapy over a minimum of 20 weeks. Contrary to their hypothesis that the two specialised treatments (CBT and IPT) would be superior to the control treatment, patients who received nonspecific clinical management had as good/ better outcome than those receiving the specialised treatments (McIntosh et al., 2005). Despite this other studies have found superior performance of CBT in increasing weight and preventing relapse in AN (Pike, Walsh, Vitousek, Wilson, & Bauer, 2003; Serfaty, Turkington, Heap, Ledsham, & Jolley, 1999), emphasising the inconsistency in the literature.

Research on drug treatments have also shown little efficacy (Brown & Keel, 2012; Bulik, Berkman, et al., 2007). For example, treatment with antidepressants has provided little evidence of weight restoration, relapse prevention, or a reduction in secondary symptoms such as anxiety or depression (Attia, Haiman, Walsh, & Flater, 1998; Ferguson, La Via, Crossan, & Kaye, 1999; Walsh et al., 2006). There is no clear evidence of effective drug treatment for core ED pathology, although atypical antipsychotics, such as

Olanzapine, have been reported to aid weight restoration (Attia et al., 2011; Bissada, Tasca, Barber, & Bradwejn, 2008; Brambilla et al., 2007), and reduce secondary symptoms such as depression, and obsession-compulsive symptoms (Bissada et al., 2008; Mondraty et al., 2005). Limited efficacy has been found for the use of atypical antipsychotics in adolescent AN (Court et al., 2010; Kafantaris et al., 2011).

This lack of evidence based treatments was reflected in the guidelines published by The National Institute for Clinical Excellence (NICE) for the treatment of EDs in 2004. These guidelines suggested there was insufficient evidence to make evidence-based recommendations for the treatment of AN. The following general recommendations were made for the treatment of AN:

A. Family–based treatments should be offered to children and adolescents.

B. Most patients with AN should be treated as outpatients

C. Inpatient services should combine refeeding with psychosocial interventions.

This paucity of effective treatments emphasises the importance of research looking at the underlying biological processes and mechanisms of behaviour in AN, in order to develop new treatment and intervention strategies. Indeed, Kaye et al (2015) have developed a neurobiologically informed treatment, Neurobiologically Enhanced With Family Eating Disorder Trait Response Treatment (NEW FED TR) (Kaye et al., 2015). NEW FED TR aims to reduce core symptoms using behavioural approaches to target AN-specific neurobiological mechanisms suggested to underpin appetite regulation in AN (i.e. anticipatory anxiety, reward insensitivity, and deficits in interoceptive awareness), although empirical data are still required to test the efficacy of this approach (Knatz, Wierenga, Murray, Hill, & Kaye, 2015).

1.6 Overview of Part 2: Compulsivity in Anorexia Nervosa

The compulsive nature of weight-loss behaviour central to AN, such as relentless self-starvation and over-exercise, has led to suggestion of parallels between AN and other compulsive disorders OCD and SUDs. As discussed in Part 1, there is a huge unmet need for effective treatments in AN, which has high rates of comorbidity and the highest mortality rate of any psychiatric disorder, yet a grave paucity of effective treatments. Viewing compulsivity as a transdiagnostic concept, seen in various manifestations across disorders, may help delineate the mechanisms responsible for the persistence of AN, and aid treatment development. Part 2 explores models of compulsivity, which suggest dysfunction in cortico-striatal neural circuitry may underpin compulsive behaviour, and considers evidence of aberrancies in this circuitry across disorders. Excessive habit formation is considered as a mechanism by which initially rewarding weight-loss behaviour in AN may become compulsive over time, and the complex balance between positive and negative reinforcement in this process is discussed. The physiological effects of starvation in promoting compulsivity, positive reinforcement and habit formation are also considered.

1.7 Compulsive behaviour in Anorexia Nervosa

Compulsivity can be defined as a trait leading to behaviour that is inappropriate to the situation, persists despite having no relationship with any overall goal, and results in undesirable consequences (Dalley et al., 2011). In individuals with AN, dietary restriction tends to take on a driven and compulsive quality. This behaviour may be motivated by an aberrant sense of reward, specifically the perceived rewards of extreme dietary control and thinness (Fladung et al., 2010; Fladung et al., 2013; Park, Dunn, & Barnard, 2011, 2012). In some individuals, such extreme control of eating and weight cannot be sustained, and AN may then be complicated by the development of binge-eating and compensatory purging such as self-induced vomiting and/or laxative abuse (Fairburn et al., 2003), which also appears to have an element of compulsivity. Excessive exercise is also a common feature, and is reported to be more prevalent in restrictive AN (80%), compared to the binge/purging subtype (43%) (Dalle Grave, Calugi, & Marchesini, 2008). Excessive exercise is described as intense driven exercise, with a compulsive nature (Mond, Hay, Rodgers, & Owen, 2006), and those who engage in driven over-exercise report feeling compelled to exercise, and feeling extreme guilt when prevented from exercising (Fairburn & Cooper, 1993). Excessive exercise is commonly used as a compensatory behaviour in AN, and is associated with a worse outcome, greater ED severity, and depression (Stiles-Shields, Bamford, Lock, & Le Grange, 2014; Stiles-Shields, Goldschmidt, Boepple, Glunz, & Le Grange, 2011; Stiles-Shields, Labuschagne, Goldschmidt, Doyle, & Le Grange, 2012). The presence of compulsive exercise in AN is extremely challenging to manage and can contribute to medically dangerous degrees of weight loss.

1.7.1 Behavioural parallels with other compulsive disorders

The compulsive behaviours seen in AN have often been compared to those of

OCD, but with the obsessional focus being on eating, weight and shape. The compulsions that characterise OCD are defined as repetitive, purposeful actions, which are often performed to reduce the anxiety caused by persistent, intrusive thoughts (Steinglass & Walsh, 2006). In the same way, individuals with AN have persistent, intrusive thoughts regarding food and weight gain, and may develop compulsive, ritualised behaviours in an attempt to neutralise the anxiety associated with these thoughts (Steinglass & Walsh, 2006).

As discussed in Section 1.4, comorbidity is found to be high between AN and OCD. The presence of obsessive compulsive symptoms is a risk factor for developing AN (Anderluh, Tchanturia, Rabe-Hesketh, Collier, & Treasure, 2008); and the level of such symptoms remains elevated to some extent even after recovery (Holtkamp et al., 2005). OCD is reported to be most prevalent in the restrictive subtype of AN (Fornari et al., 1992; Lilenfeld et al., 1998), although reported prevalence has been inconsistent across studies (Godart et al., 2002). Familiality is reported, with the first degree relatives of individuals with AN showing an elevated risk for OCD (Bellodi et al., 2001), and candidate gene studies suggest common genetic liability between the two disorders (Mas et al., 2013). Comorbidity with Obsessive-Compulsive Personality Disorder (OCPD) is also high (Lilenfeld, Wonderlich, Riso, Crosby, & Mitchell, 2006), and the excessive self-control (Pinto, Steinglass, Greene, Weber, & Simpson, 2014), perfectionism and rigidity seen in OCPD (Ansell et al., 2010) may parallel AN more closely.

Aspects of compulsive behaviour characteristic in AN have increasingly been compared to the compulsive drug-seeking behaviour seen in substance dependence (Barbarich-Marsteller et al., 2011; Kaye, Wierenga, Bailer, Simmons, Wagner, et al., 2013; Scheurink, Boersma, Nergardh, & Sodersten, 2010; Zink & Weinberger, 2010). The developmental period of onset is similar, with an initial phase of reward seeking, in the

form of weight loss in AN, which is experienced as rewarding and pleasurable (Park et al., 2011, 2012; Scheurink et al., 2010), as if it were a drug. This is followed by a narrowing of the behavioural repertoire, and an inability to cease behaviours despite adverse consequences (Kalivas & Volkow, 2005). The compulsive drug-seeking behaviour of addicts may parallel the relentlessness with which individuals with AN pursue weight loss. Individuals find it increasingly difficult to refrain from weight loss behaviour such as restriction and compulsive exercise despite adverse consequences (Barbarich-Marsteller et al., 2011). As discussed in Section 1.4, there is a higher incidence of substance dependence in ED than the general population However, a lower incidence of substance use has been reported in restrictive AN compared to EDs involving binge/purge behaviours, suggestive of a specific relationship between binge/purge behaviours and substance use/dependence.

Despite behavioural similarities and comorbidity, there are notable distinctions in information processing between AN, OCD, and substance dependence. In AN, an increased focus on delayed gratification and long term goals is seen (Kaye, Wierenga, Bailer, Simmons, Wagner, et al., 2013). This is reflected in marked differences in the ability to delay reward in AN as compared to substance dependence. Substance dependent individuals and those with BED show a preference for smaller immediate reward (Davis, Patte, Curtis, & Reid, 2010), whereas individuals with AN favour delayed larger rewards (Steinglass, Figner, et al., 2012). That said, starvation in those vulnerable to AN may produce an immediately rewarding sense of control (Park et al., 2012), acting as a positive reinforcer of behaviour. Equally, avoiding negative consequences such as dysphoric mood during refeeding, which some individuals with AN may experience as 'withdrawal symptoms' from starvation, may be important short term goals. Perhaps as a consequence of these immediate reinforcers, the long term goal of weight loss becomes irrationally overvalued (Barbarich-Marsteller et al., 2011). Interestingly, individuals with OCPD are

more able to delay reward than those with OCD, and this ability to delay reward is associated with perfectionism and rigidity (Pinto et al., 2014). This supports the suggestion that AN may parallel OPCD more closely than OCD. That said, studies looking at decision making processes in AN, OCD and substance dependence suggest a tendency to make disadvantageous decisions when choosing between immediate or long terms gains in all three disorders (Lawrence et al., 2006; Tchanturia, Liao, et al., 2007; Verdejo-Garcia et al., 2007). This impairment in decision making is suggested to be linked to the compulsive and self-destructive behaviour seen across these disorders (Tchanturia, Liao, et al., 2007). Whilst individuals with AN may show the ability to delay reward in general, their impairment in decision making may lead them to engage in compulsive weight loss behaviours despite adverse outcomes.

1.7.2. Section Summary

Compulsive weight-loss behaviours, such as persistent food restriction and excessive exercise, are prominent features of AN, and appear in some ways to parallel the compulsive behavioural inherent in OCD and substance dependence, with comorbidities reported. Differences in information processing between the disorders may help to explain the different manifestation of compulsivity across disorders, with the ability to delay reward in AN contrasting with the desire for immediate reward in substance dependence. If the similarities in behaviour reflect parallels in underlying mechanisms that drive this behaviour, there should be some agreement in the neurobiological correlates across these disorders, which will be discussed in the next section.

1.8 The Neural Basis of Compulsivity

Models of the neurocircuitry involved in compulsive behaviour suggest the involvement of a cortico-striatal circuit, consisting of a striatal and prefrontal component (Brewer & Potenza, 2008; Fineberg et al., 2010; Robbins, 2007). The striatal component is seen as responsible for driving compulsive behaviour, while the prefrontal component controls or inhibits this behaviour. Abnormalities in either of these components (hypoactivity/hyperactivity) may result in an increase in compulsive behaviour. The caudate nucleus (the striatal component) is suggested to drive compulsive behaviour, with the orbitofrontal cortex (OFC, the prefrontal component) exerting inhibitory control over these. This is distinct but related to an 'impulsive' cortico-striatal circuit, involving the ventral striatum (VS)/NAc (striatal component), and the anterior cingulate (ACC)/ventromedial prefrontal cortex (vmPFC; prefrontal component). Figure 1.1 illustrates these neural circuits. These compulsive and impulsive circuits are suggested to be intercommunicating, with the possibility that abnormalities in one circuit lead to abnormalities in the other (Fineberg et al., 2010). This is relevant for theories of substance dependence in which it is suggested that what may begin as impulsive behaviour may eventually become compulsive with repetition of behaviour, with a corresponding shift in control from impulsive to compulsive neural circuitry (Everitt & Robbins, 2005). This may also relate to EDs involving binge/purge behaviours, in which these behaviours may initially be driven by impulsivity, and become compulsive over time.

The involvement of a compulsive cortico-striatal circuit can be illustrated using tasks which are thought to measure compulsivity. Failures in reversal learning (i.e. the ability to adapt behaviour following negative feedback) have been suggested to reflect cognitive inflexibility, defined as a rigid cognitive style, which may contribute to compulsivity (Fineberg et al., 2010). Reversal learning is impaired by lesions to the OFC

(Berlin, Rolls, & Kischka, 2004; Dias, Robbins, & Roberts, 1996; Remijnse et al., 2006), an area selectively activated during reversal learning tasks (Hampshire & Owen, 2006). Lesions to the medial striatum have also been shown to produce impairments in reversal learning in monkeys (Clarke, Robbins, & Roberts, 2008), supporting the suggestion that a cortical and striatal component is involved in compulsive behaviour. Set-shifting tasks, in which attention is required to switch between multiple tasks, or elements of a task (Miyake et al., 2000), is also thought to measure cognitive inflexibility (Fineberg et al., 2010). Lesions to the lateral PFC in primates (Dias et al., 1996) and the ventrolateral PFC in humans (Hampshire & Owen, 2006) impair performance on set-shifting tasks. Failures in both these types of task, and the corresponding neuroanatomy, suggest that impairments in 'top down' cortical control may underpin compulsive behaviour, and over activity of striatal regions may also underpin, or exacerbate compulsivity.

Figure 1.1. Neural Circuits of Compulsivity and Impulsivity

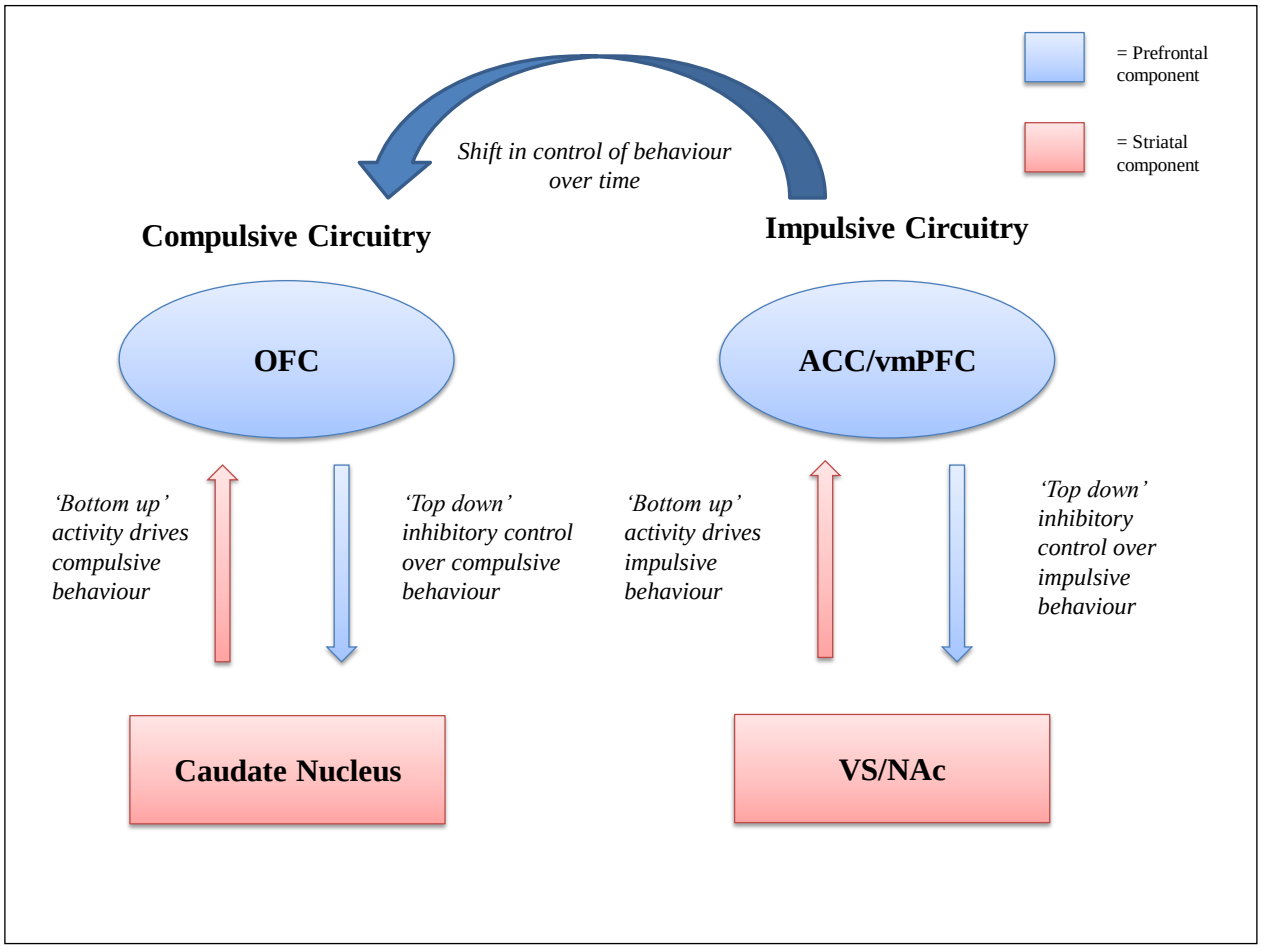


Figure 1.1.

Representation of the cortico-striatal circuitry driving compulsive and impulsive behaviour (Brewer & Potenza, 2008; Fineberg, et al., 2010; Robbins, 2007). In both circuits activity the striatal component drives behaviour, whilst the prefrontal component inhibits behaviour. Both failures in 'top down' control of the prefrontal components, and over activity of 'bottom up' striatal activity can result in increases in compulsive or impulsive behaviour. These circuits are suggested to be intercommunicating, with abnormalities in one circuit potentially leading to abnormalities in the other circuit. Models of addiction suggest that what begins as impulsive behaviour may transition with repetition over time to become compulsive, which is reflected in a shift of control from corresponding impulsive to compulsive neural circuitry (Everitt & Robbins., 2005, Robbins et al., 2012).

1.8.1 Are the neural correlates of compulsivity observed in Anorexia Nervosa and other compulsive disorders?

Dysfunction of the neurocircuitry implicated in compulsivity can be seen across AN, OCD and addiction. In terms of a dysfunctional striatal component, AN has been associated with increased caudate function, measured both directly during a monetary reward task (Wagner et al., 2007), and indirectly during exposure to aversive food stimuli (Cowdrey et al., 2011). In OCD, increased functional connectivity within the cortico-striatal circuitry is shown to correlate positively with Y-BOCS score (Hou et al., 2013), a measure of obsessive-compulsive symptoms. Evidence of increased activity in the caudate nucleus (Saxena, Brody, Schwartz, & Baxter, 1998), and alterations in caudate volume have also been reported in OCD (Scarone et al., 1992). In contrast to AN and OCD, chronic substance use has been associated with decreased activation of the caudate during reward anticipation (van Hell et al., 2010). However, high scores on self-reported food addiction have been associated with increased activation in the caudate (Gearhardt, Yokum, et al., 2011), suggesting there may be differences in caudate activation between behavioural and substance addictions.

Decreased activation of a prefrontal component can also be seen across disorders. Reduced activity in the OFC whilst viewing disorder-related stimuli has been shown in AN (Uher et al., 2004), and alterations in OFC volume have been reported (Frank, Shott, Hagman, & Mittal, 2013). Reduced activation of the OFC during reversal learning has also been found in individuals with OCD and their unaffected relatives (Chamberlain et al., 2008), and abnormalities in OFC gray matter are reported in both OCD (Menzies et al., 2008), and substance dependence (Franklin et al., 2002). Furthermore, reduced functional connectivity of the right inferior and superior OFC was associated with both self-reported compulsivity in OCD, and compulsive drug taking in substance dependence (Meunier et al., 2012).

Abnormalities in the 'compulsive' circuit are implied by deficits in the neuropsychological tasks discussed in Section 1.7, thought to tap this construct (see Table 1.1). Individuals with AN are often described as having low cognitive flexibility (Tchanturia et al., 2004), and consistently show poor set-shifting abilities (Bühren et al., 2012; Holliday, Tchanturia, Landau, Collier, & Treasure, 2005; Steinglass, Walsh, & Stern, 2006). Poor set-shifting has been suggested as an endophenotype of both AN and BN, and is associated with both longer illness duration and increased disorder-related rituals (Roberts, Tchanturia, & Treasure, 2010). Impairments in reversal learning have also been reported in AN, and are shown to occur before and after weight gain (Hildebrandt et al., 2015; Sarrar et al., 2011), suggesting this is a trait rather than state-related impairment. OCD and substance dependence have also both been associated with deficits in reversal learning (Chamberlain et al., 2008; Izquierdo & Jentsch, 2012; Remijnse et al., 2006; Valerius, Lumpp, Kuelz, Freyer, & Voderholzer, 2008), and set-shifting (Fontenelle, Marques, Engelhardt, & Versiani, 2001; Lawrence et al., 2006; Saraswat, Ranjan, & Ram, 2006).

Table 1.1 Evidence of abnormalities in the neurocircuitry, neurotransmitters and behavioural correlates of compulsivity, across AN, OCD and Addictions.

	Model of compulsivity	Evidence in AN	Evidence in OCD	Evidence in Addictions
Neurocircuitry	• Fronto-striatal circuit involving the OFC (prefrontal component) and the caudate nucleus (striatal component) (Fineberg et al, 2010; Robbins, 2007; Brewer & Potenza, 2008). • Abnormalities result from impairments in prefrontal inhibitory control OR over activity of the striatal component. (Fineberg et al, 2010; Robbins, 2007; Brewer & Potenza, 2008).	• Increased caudate function during reward task (Wagner et al, 2007), and exposure to aversive food stimuli (Cowdrey et al, 2011). • Decreased OFC activity during disorder related stimuli (Uher et al, 2004); decreased OFC volume (Frank et al, 2013). • Deactivation of fronto-striatal circuitry predicted by levels of compulsivity (Rothemund et al, 2011).	• Increased FC of CTSC circuits correlated with Y-BOCS scores (Hou et al, 2013). • Increased volume and activity in caudate (Hou et al, 2013; Saxena et al, 1998; Scarone et al, 1992) • Reduced activation of OFC during reversal learning (Chamberlain et al, 2008); abnormalities in OFC grey matter (Menzies et al, 2008); reduced FC of OFC (Meunier et al, 2012).	• Decreased activation of caudate during reward anticipation (van Hell et al, 2010). • Behavioural addiction associated with increased activation of caudate (Geardhart et al., 2011) • Abnormalities in OFC grey matter (Menzies et al, 2008); reduced functional connectivity of OFC (Meunier et al, 2012).
Neurotransmitter	• Role for serotonin and 5-HT receptors: Impairments in reversal learning linked to reduced serotonin (Evers et al, 2005; Clarke et al, 2004); antagonising 5HT-2A receptors impairs reversal learning (Boulougouris et al, 2008). • Role for the mesolimbic dopamine system: DA tone in the ventral	• Increased 5HT-1A and decreased 5HT-2A binding potential (Bailer et al, 2007; Kaye et al, 2005; Kaye et al, 2005). • Altered striatal DA release in recovered AN: increased binding of DA D2/3 receptors in anterior VS (Frank et al, 2005; Bailer et	• Agonising 5HT-2C and 1B receptors increases compulsivity in OCD (Tsaltas et al, 2005; Hollander et al 1991; Gross-Isseroff et al, 2004). • DA D2 receptor agonists linked to repetitive checking behaviour in rodents (Pitman, 1989; Tizabi et al, 2002).	• Antagonising 5HT-2A and agonising 5HT-2C receptors prevents relapse in rodents (Fletcher et al, 2002; Pentowski et al, 2010); antagonising 5HT-1B receptors inhibits cocaine seeking in rodents (Miskiel et al, 2011). • Initial reinforcing effect of drugs associated with release of

	loops important in regulating reward and reinforcement (Wise, 2002; Fineberg et al, 2010); DA D2 receptor agonists associated with impairments in reversal learning (Cools et al, 2006), and increased compulsive behaviour (Voon et al, 2009); • Modulation of glutamate by DA involved in reward processes (Guardia et al, 2011); glutamate involvement in set shifting (Nicolle & Baxter, 2003).	al, 2013); DA release experienced as anxiogenic (Bailer et al, 2012). • DA D2 receptor polymorphism linked to AN (Bergen et al, 2005). • Reduced HVA in CSF in recovered AN (Kaye et al, 1999), increased levels in acute AN (Castro-Fornieles et al, 2008); • Increased CSF glutamate in AN (Nakazato et al, 2010).	• Successful use of antipsychotics in treating OCD patients (Cavedini et al, 2004). • Increased levels of DA in the striatum (Perani et al, 2008); • Increased CSF glutamate in OCD patients; efficacy of drugs that act on GABA and glutamate pathways (Pittenger et al, 2011).	extracellular DA in striatum (Koob & Voljowm, 2010). • Decreased activity in mesolimbic DA system with chronic use (Volkow et al, 2007); Decreased DA D2 receptors and DA release in striatum. (Volkow et al, 2002); • Efficacy of drugs that act on GABA and glutamate pathways (Kenny & Markou, 2004).
Behavioural tasks	• Impairments in cognitive flexibility tasks such as reversal learning (Fineberg et al, 2010), associated with OFC (Dias et al, 1996; Berlin et al, 2004; Remijnse et al, 2006) and medial striatal abnormalities (Clarke et al, 2008), and set-shifting (Fineberg et al, 2010) associated with PFC abnormalities (Dias et al, 1996; Hampshire & Owen, 2006).	• Low in cognitive flexibility (Tchanturia et al, 2004). • Impairments on set-shifting tasks (Holliday et al, 2005; Steinglass et al, 2006; Buhren et al, 2012). • Subtle impairments in reversal learning (Sarrar et al, 2011; Hildebrandt et al, 2015).	• Impairments on set-shifting (Lawrence et al, 2006; Fontenelle et al, 2001) and reversal learning tasks (Chamberlain et al, 2008; Valerius et al, 2008; Remijnse et al , 2006).	• Impairments on set-shifting (Saraswat et al, 2006) and reversal learning tasks (Izquierdo and Jentsch, 2012).

Note: OFC = Orbitofrontal Cortex; CTSC = Cortico-thalamo-striatal circuit; Y-BOCS = Yale-Brown Obsessive Compulsive Scale; 5-HT = 5- hydroxytryptamine; DA = Dopamine; VS = Ventral Striatum; HVA = Homovanillic acid; CSF = Cerebrospinal Fluid; GABA = Gamma-amino butyric acid; FC = Functional Connectivity

1.8.2 Neurotransmitter dysfunction across compulsive disorders

Serotonin

Serotonin has widespread effects on satiety, impulse control and mood, with evidence for a specific role for 5-HT receptors in compulsive behaviour (See Table 1.1). A rodent model of OCD indicates that 5-HT-2C receptor agonists increase compulsivity, or the persistence of behavioural response in these rats (Tsaltas et al., 2005). This result has been replicated in exacerbating compulsive symptoms in human OCD patients (Hollander et al., 1991), in whom 5-HT-1B receptor agonists also exacerbate OCD symptoms (Gross-Isseroff, Cohen, Sasson, Voet, & Zohar, 2004). Impairments in reversal learning have been linked to reduced brain serotonin (Evers et al., 2005), particularly in areas such as the OFC (Clarke, Dalley, Crofts, Robbins, & Roberts, 2004), and antagonism of 5-HT-2A receptors impairs reversal learning (Boulougouris, Glennon, & Robbins, 2008), indicating their involvement in the development of compulsive behaviour.

The 5-HT system has been extensively studied in AN, with much evidence of dysfunction in this system. Imaging studies have consistently shown increased 5HT-1A and decreased 2A receptor binding potential in individuals both currently ill and recovered from AN (Bailer et al., 2007; Kaye, Frank, Bailer, & Henry, 2005; Kaye, Frank, Bailer, Henry, et al., 2005; Kaye, Wierenga, Bailer, Simmons, & Bischoff-Grethe, 2013), suggesting a trait and not state related alteration. Interaction between 5HT-1A and 2A receptors in the medial prefrontal cortex (mPFC) have been suggested to modulate impulsivity and compulsivity (Carli, Baviera, Invernizzi, & Balducci, 2006), although there is yet to be evidence of this mechanism underpinning the development of compulsive behaviour in AN.

The 5-HT system is modulated by many drugs of abuse (Kirby, Zeeb, &

Winstanley, 2011). Research in this area is extensive, the scope of which cannot be covered in this review. However, evidence to date points to a particular role for 5HT-2A and 2C receptors in relapse during withdrawal, and in the persistence of compulsive drug-seeking in addiction (Fletcher, Grottick, & Higgins, 2002; Pentkowski et al., 2010). Furthermore, there is an inhibitory effect of 5-HT-1B receptor antagonists on cocaine-seeking behaviour (Miszkiel, Filip, & Przegalinski, 2011). In terms of behavioural addictions, peripheral measures suggest reduced serotonin levels in pathological gamblers (Nordin & Sjödin, 2006). This was hypothesised to be linked to maladaptive decision making in these individuals (Kirby et al., 2011), and treatment with SSRIs has been shown to be effective (Hollander & Rosen, 2000).

Although aberrancies in the 5-HT system are seen across compulsive disorders, these do not appear to be universal in nature, suggesting that the serotonergic neurotransmitter system alone is unlikely to be driving compulsive behaviour.

Dopamine

Dopamine (DA) is considered key to the rewarding effects of both natural and drug-derived rewards (Volkow, Wang, Fowler, Tomasi, & Baler, 2012), and the mesolimbic DA pathways in particular play a crucial role in reward and reinforcement processes (Wise, 2002). Models of compulsivity have emphasised the importance of DA tone in the ventral loops that link the ventral ACC and the VS/NAc in regulating reward and reinforcement behaviours (Fineberg et al., 2010). DA D2 receptor agonists such as levo-dopa have been associated with deficiencies in reversal learning (Cools, Altamirano, & D'Esposito, 2006), and increased compulsive behaviour in Parkinson's disease (Voon et al., 2009). Studies in animals have also shown that the administration of DA agonists induces stereotyped behaviours associated with OCD (Pitman, 1989). Specifically, the use

of a selective D2 receptor agonist in rats was associated with the development of repetitive checking behaviour (Tizabi et al., 2002). DA dysfunction in OCD patients is also indicated by the successful use of antipsychotics when SSRI treatment is unsuccessful (Cavedini, Bassi, Zorzi, & Bellodi, 2004). There have also been reports of increased levels of DA in the striatum in OCD (Perani et al., 2008).

A key process in the initial reinforcing effect of drugs is their ability to produce increases in extracellular DA in limbic regions such as the NAc/VS (Koob & Volkow, 2010). This release of DA is associated with a feeling of euphoria, and is experienced as rewarding (Volkow et al., 1996), thus positively reinforcing their use. The expectation of drug reward (i.e. in certain contexts) is also important in reinforcing drug use (Volkow et al., 2003), and is likely to depend on neurotransmitters such as glutamate, which is known to modulate DA release in the NAc (Kalivas & Volkow, 2005). These DA- dependent effects cause drugs themselves, and drug-associated stimuli, to gain incentive salience and promote further drug-seeking behaviour (Everitt & Robbins, 2005). This repeated and prolonged DA increase results in synaptic changes in DA pathways, and these changes may be responsible for the formation of compulsive habits that persist despite adverse consequences in substance dependence (Wolf, 2002).

In substance dependent individuals, activity in the mesolimbic DA system is decreased, a deficiency that persists for months following detoxification (Volkow, Fowler, Wang, Swanson, & Telang, 2007). Chronic cocaine abusers are shown to have decreased levels of D2 receptors and a decrease of DA release in the striatum (Volkow, Fowler, & Wang, 2002), despite initial drug use being associated with synaptic increases in DA (Volkow et al., 2007). Evidence of decreased DA activity following chronic drug use has led to the suggestion that this deficiency in DA may cause an increase in the compulsion to seek further drug reward to order to increase deficient DA levels, with repetition of this

behaviour leading to a dependence on the substance (Fineberg et al., 2010). In contrast, individuals recovered from AN have increased binding of DA D2/D3 receptors in the anterior VS (Frank et al., 2005), while currently ill AN patients has shown increased levels of the DA metabolite homovanillic acid (HVA) in cerebrospinal fluid (Castro-Fornieles et al., 2008). The increased DA receptor binding in recovered AN patients contrasts with the reduced striatal DA binding found in those with substance abuse (Volkow, Fowler, Wang, Baler, & Telang, 2009; Volkow, Wang, Fowler, & Tomasi, 2012), which is paralleled by those with BN (Broft et al., 2012), and obesity (Kenny, 2011). Striatal DA response has been negatively associated with binge eating and vomiting (Broft et al., 2012), suggesting that individuals who engage in overeating may have reduced DA function, similar to that found in substance dependence.

DA release in the dorsal putamen is associated with anxiety in recovered AN, which contrasts with the euphoria reported by controls (Bailer et al., 2012). Palatable food ingestion is associated with DA release in the striatum (Bassareo & Di Chiara, 1999), suggesting that individuals with AN may experience this DA release as aversive, as opposed to the hedonic response seen in healthy controls. This aversive reaction to food may explain the relentless food restriction seen in AN, which may be experienced as anxiolytic (Kaye, Wierenga, Bailer, Simmons, Wagner, et al., 2013).

Glutamate

Glutamate is the principal excitatory neurotransmitter in the brain and is involved in many cognitive functions such as memory and learning (Jamain et al., 2002). The mesolimbic DA system, central to brain reward processes and compulsivity, has a variety of excitatory glutaminergic and inhibitory gamma-amino butyric acid (GABA, of which glutamate is the precursor) inputs (Guardia, Rolland, Karila, & Cottencin, 2011). The

NAc, a region heavily implicated in reward processes, has glutaminergic inputs from limbic regions, and GABAergic projections to other reward-related areas (Guardia et al., 2011). There is extensive physiological and neurochemical evidence to suggest that reward-related learning requires an interaction between DA and glutamate, and occurs as the result of modulation by DA of glutamate synapses in the striatum (Beninger & Gerdjikov, 2005). Alterations in glutamate receptor binding in the cingulate cortex and dorsal striatum have been associated with impairments in set shifting ability (Nicolle & Baxter, 2003), further suggesting a role for glutamate in cognitive flexibility and compulsivity.

DA modulation of glutamate has been implicated in the development and expression of addictive behaviours, and evidence suggests that modulation of GABA and glutamate pathways may be effective in the treatment of substance use disorders (Olive, Cleva, Kalivas, & Malcolm, 2012). Animal studies have shown the efficacy of GABA agonists in attenuating the positive reinforcing effects of drugs, and glutamate antagonists may be effective in preventing relapse (Kenny & Markou, 2004). Drugs modulating glutaminergic and GABAergic pathways have also been shown to act on binge eating, purging and weight loss in EDs (Guardia et al., 2011). Interestingly, both OCD and AN are associated with an increase in cerebrospinal fluid glutamate (Nakazato et al., 2010; Pittenger, Bloch, & Williams, 2011). Although successful treatment with glutaminergic drugs has yet to be reported in AN, some improvement has been found in the treatment of OCD (Pittenger et al., 2011).

1.8.3 Section Summary

Models of compulsivity suggest neurocircuitry involves both striatal and prefrontal components, with the 'bottom up' striatal component driving compulsive behaviour, and

the'top down' prefrontal component inhibiting this behaviour. Abnormalities in either or both of these components may lead to increases in compulsive behaviour. Dysfunction in this circuitry and tasks reported to reflect activity in these regions can be seen across AN, OCD and substance addictions, and abnormalities in neurotransmitter activity linked to impulse control and reward, serotonin, DA and glutamate, are also seen across these disorders. Together these results point to possible shared neural underpinnings for compulsive behaviour, which become disorder specific in their manifestation.

1.9 The Habit Hypothesis of Compulsive Behaviour

Compulsivity, as previously defined, can also be described as a tendency to carry out repetitive acts in a habitual manner (Fineberg et al., 2010). Habits are described as behaviours that are not innate, are engaged in repeatedly and become fixed, occur without conscious effort, and can be elicited by external stimuli (Graybiel, 2008). Two distinct types of learning are involved in the acquisition of behaviour: action-outcome learning and stimulus-response learning (Robbins, Gillan, Smith, de Wit, & Ersche, 2012). Action-outcome learning (also referred to as goal-directed learning) occurs when a particular action leads to a rewarding outcome. If at any point the action no longer leads to reward, the frequency of that action will decrease (Balleine & O'Doherty, 2010). However, if these new actions are engaged in repeatedly (over-trained), they may become insensitive to the outcome, and will be repeated even when no longer result in reward (stimulus-response learning). In this way, behaviour that begins as goal-directed may become a stimulus-response habit when repeated over time (Graybiel, 2008). Despite the suggested distinction between goal-directed and habit learning, early description of habits describe them as a form of automatic goal-directed behaviour. Bargh (1989) suggests that habits form as the instrumental link between goals and actions, and are automatically activated when a relevant goal is present (Bargh, 1989). This may be particularly relevant for disorders such as AN, in which automatic habits, which take the form of compulsive weight-loss behaviours, may occur unconsciously in the persistent presence of long term weight-loss goals.

Research indicates neural distinctions between goal-directed and habit learning. In humans, the ventromedial PFC has been linked to goal directed learning (Daw, Niv, & Dayan, 2005), while the putamen has been linked to habit learning (Tricomi, Balleine, & O'Doherty, 2009). Cortico-striatal connectivity- as indexed by Diffusion Tensor Imaging

(DTI), which measures the strength of white matter tracts- has been associated with differences in habit and goal-directed control of actions (de Wit et al., 2012). In a behavioural learning task, the tendency to rely on habits was associated with white matter tract strength between the premotor cortex and posterior putamen, and grey matter density in the posterior putamen; while the tendency to use goal directed control was associated with tract strength in the ventromedial PFC from the caudate (de Wit et al., 2012). Further research has shown a bias towards habit formation in a decision making task was associated with lower grey matter volume in the caudate and medial OFC (Voon et al., 2014). The cortico-striatal circuitry implicated in habit vs goal directed behavioural control is similar to that suggested in models of the neurocircuitry of compulsivity, supporting the suggestion that compulsive behaviour may be underpinned by habitual control of behaviour, as these constructs appear to be indexed by overlapping neurocircuitry. Investigating abnormalities in habit learning and related brain areas may thus further understanding of the development of compulsive behaviour across disorders.

1.9.1 Is excessive habit formation observed across compulsive disorders?

Emergent evidence suggests that dysregulation of habit formation may provide a mechanism by which the development of well-entrenched, compulsive behaviours can occur. For example, once drug taking is engaged in repeatedly, it becomes associated with a number of environmental stimuli or cues, which thereby become triggers for compulsive drug-seeking and drug taking, despite knowledge of the negative consequences of engaging in this behaviour (Belin, Economidou, Pelloux, & Everitt, 2011). Habit learning may also play a role in disorders such as AN and OCD, in which certain compulsive, and sometimes ritualistic, behaviours may persist despite a lack of reward or intermittent reward, and a wide variety of negative consequences (Steinglass & Walsh, 2006).

The development of substance dependence has been described in terms of a transition from initially goal-directed drug taking, driven by the reinforcing properties of the drug, to progressively more compulsive drug-seeking controlled by the habit system (Everitt & Robbins, 2005), and ultimately driven by environmental stimuli associated with the drug (Belin et al., 2011). Animal models of compulsive drug-seeking have investigated habit formation using outcome devaluation paradigms, in which previously rewarding action-outcome contingences are devalued, and persistence of behaviour despite this devaluation is measured. These demonstrate that reinforcement with cocaine, in comparison to a natural reward such as lemon-sucrose solution, result in accelerated habit learning, and less sensitivity to devaluation (Miles, Everitt, & Dickinson, 2003). Similar results have been found with other drugs of abuse, such as alcohol (Dickinson, Wood, & Smith, 2002), suggesting that the reinforcing effects of drugs may promote dominance of the habit system in learning and result in the development of compulsive drug seeking behaviours. Everitt and Robbins (2005) support this idea with a neural systems model of substance dependence, in which this transition from goal directed to habitual control represents a change from prefrontal cortical to striatal control, and a progression from ventral to dorsal areas of the striatum (Everitt & Robbins, 2005). This is further supported by rodent studies (Ito, Dalley, Howes, Robbins, & Everitt, 2000; Ito, Dalley, Robbins, & Everitt, 2002), and data from human cocaine addicts showing increased dorsal striatum activity during presentation of drug cues (Volkow et al., 2006). Data from human studies has also shown a reliance on stimulus-response habits in substance dependence (Sjoerds et al., 2013; Voon et al., 2014), as well as decreased activity in regions associated with goal directed behaviour (vmPFC and anterior putamen), and increased recruitment of areas associated with habitual control (posterior putamen) (Sjoerds et al., 2013). Drugs of abuse may also decrease the ability of the individual to exert control over these habits, even

when presented with persistent negative and aversive consequences (Deroche-Gamonet, Belin, & Piazza, 2004). A parallel can be drawn here with the compulsive behaviours seen in AN: Individuals with AN often report wanting to recover from their disorder, despite persisting with compulsive behaviour that maintains their emaciation.

Binge-eating behaviour in obesity has also been associated with a tendency towards habitual control of behaviour (Voon et al., 2014). The relationship between obesity and SUDs has received increasing interest, with suggestion that obesity results from an addiction to food that strongly resembles addiction to drugs. This is supported by evidence from animal models in which highly palatable foods can be used to induce addiction-like phenotypes in rats (Avena, Rada, & Hoebel, 2008). Recent research suggests this similarity may be underpinned by a shared tendency towards habitual control of behaviour, accompanied by shared caudate and orbitofrontal grey matter abnormalities (Franklin et al., 2002; Morales, Lee, Hellemann, O'Neill, & London, 2012; Voon et al., 2014), areas which were associated with habit formation in healthy controls (Voon et al., 2014).

Compulsive behaviour in OCD has also been associated with over-reliance on habits in learning (Gillan et al., 2013; Gillan et al., 2011; Voon et al., 2014). Gillan et al (2011) showed that individuals with OCD had a selective impairment in goal-directed control of behaviour which forced them to rely on previously learned habits. Although individuals with OCD showed no overall impairment in using feedback to guide learning, they showed weaker knowledge of the direct causal relationship between actions and outcomes, leading to errors. Symptom severity was predictive of persistent responding to devalued stimuli, suggesting the continued use of previously learned habits may be related to the severity of compulsions (Gillan et al., 2011). Using a shock avoidance paradigm, Gillan et al (2013) also demonstrated that individuals with OCD have a tendency to develop excessive *avoidance* habits (Gillan et al., 2013). Further research using trial-by-

trial learning, rather than the overtraining on simple stimulus-response contingencies, also found deficits in goal-directed behaviour, and indicated that a tendency to rely on habits in OCD may reflect a disturbance in the goal-directed system (Voon et al., 2014).

Recent studies have looked at the neural underpinning of excessive habits in OCD. Gillan et al (2015) reported that excessive habit formation in OCD was associated with hyperactivation in the caudate, which correlated with the subjective urge to perform habits in this task (Gillan et al., 2015). Furthermore, they found hyperactivation of the medial OFC during the acquisition of the habit response, supporting previous evidence of the involvement of the OFC and caudate in habit formation (de Wit et al., 2012; Voon et al., 2014). In a subsequent study, Banca et al (2015) used a task that measured avoidance responses to individualised real-time symptom provocation in OCD, thus potentially capturing avoidance responses to previously formed habits. Although this task did not directly involve assessment of learning processes, deactivation of caudate-prefrontal circuits, and hyperactivation of the subthamalmic nucleus and putamen, were observed during strong symptom provocation (Banca et al., 2015). This is in line with suggested cortical-striatal dysfunction in the development of habits. Furthermore, hyperactivation of the putamen during symptom provocation subsequently deactivated following an avoidance response, supporting the role of the putamen in the control of habitual behaviour (Banca et al., 2015).

Walsh (2013) elegantly outlines the mechanisms by which aberrant habit formation may contribute to the maintenance of AN. It is suggested that restrictive eating may begin as the result of goal-directed weight-loss behaviour, in which behaviour becomes associated with a rewarding outcome (weight loss). If this restrictive eating behaviour is repeated enough it may become relatively insensitive to reward. In this way, weight-loss behaviour becomes highly practiced and over-trained, and weight loss as a rewarding

outcome may be needed only intermittently, or even no longer necessary for this behaviour to continue. The fact that habitual behaviour is outcome-independent makes it highly resistant to change, reflecting the treatment resistance often seen in individuals with AN (Walsh, 2013). It is further suggested that during the process of habit formation in AN, restrictive behaviour itself becomes rewarding through conditioned reinforcement (Walsh, 2013), in which a set of cues begin to develop, and take on rewarding properties themselves (Everitt & Robbins, 2005). Individuals with AN may thus start to find that the reward of weight loss is no longer required as the now habitual weight loss behaviours themselves and associated cues have become rewarding or reinforcing. This process is also seen in substance dependence, in which cues associated with drug taking become associated with craving for the drugs and drug taking (Wikler, 1973).

Rothemund et al (2011) reported that high levels of compulsivity in severely low weight AN patients predicted deactivation of the fronto-striatal circuitry whilst viewing food pictures. This finding was interpreted as reflecting the transition from goal-directed actions to the development of habitual compulsive behaviour (Rothemund et al., 2011), similar to that described in substance dependence (Everitt & Robbins, 2005). During the high calorie picture condition in this study, individuals with AN showed increased activation in the right caudate and right precuneus, suggested to reflect increased habit learning processes compared to control participants. Furthermore, reduced grey matter volume in the bilateral OFC, and the right middle and superior frontal gyrus was found in individuals with AN, indicative of dysfunctional goal-directed behavioural control (Rothemund et al., 2011). The results of this study suggest aberrancies in the neurocircuitry associated with goal directed actions and habits in AN, which may reflect the persistence of compulsive weight-loss behaviours in this disorder.

1.9.2 Section Summary

Excessive reliance on habits in learning may underpin the development of compulsive, habitual behaviours and emergent evidence suggests an overreliance on habits in both OCD and substance dependence. Models of addiction suggest a transition over time from initially goal-directed behaviour to compulsive, habitual behaviour which is reflected in a shift of control in corresponding neural circuitry, from prefrontal to striatal, and from ventral to dorsal striatum. Although recent theory implicates excessive habit formation in the development of compulsive weight-loss behaviours in AN, there is to date no published evidence to support this theory. Investigation of habit formation as a possible mechanism by which compulsive behaviour develops in AN may guide novel treatment development targeting this behaviour.

1.10 The role of positive and negative reinforcement in compulsivity

Whilst AN and OCD have often been conceptualised as disorders driven by avoidance and fear of weight gain in AN, and of disorder-related obsessions in OCD, substance dependence is commonly thought to be driven by an approach response, to gain the rewarding effects of drugs. If compulsive behaviour is driven by a common process in these disorders, there should be some coherence in the reinforcement processes maintaining compulsive behaviour.

1.10.1 Positive and negative reinforcement in Anorexia Nervosa

AN has often been associated with anhedonia and a negative mind-set, with the suggestion that compulsive self-starvation serves to reduce the anxiety and negative affect that becomes associated with food (Kaye et al., 2003; Wildes, Ringham, & Marcus, 2010; Zink & Weinberger, 2010). Indeed, food ingestion may be experienced as anxiogenic for individuals with AN (Bailer et al., 2012). This may provide one mechanism through which individuals with AN experience self-starvation as a relief from this food associated anxiety (Kaye et al., 2003), and indicates that negative reinforcement plays a role in the maintenance of AN. Furthermore, compulsive exercise behaviour has been associated with high levels of anxiety and depression in AN, and may serve as a means of reducing these negative states (Meyer, Taranis, Goodwin, & Haycraft, 2011).

However, the maintenance of restrictive behaviour in AN may also involve positive reinforcement processes. Selby et al (2013) suggest a model in which positive emotions associated with successful weight loss, such as feelings of pride and accomplishment, reinforce and drive further weight loss behaviour. Over time, weight-loss behaviour is conditioned to elicit positive emotions regardless of whether further weight loss is attained (Selby et al., 2013). The underlying premise of this theory is consistent with that of

Walsh's (2013) habit formation theory, which suggests weight-loss behaviour is conditioned to take on rewarding properties over time (Walsh, 2013). Evidence that weight-loss behaviour in AN may be driven by positive reinforcement also comes from a series of fMRI studies. Fladung et al (2010) found that positive feelings and increased activation in the VS were associated with underweight pictures in individuals with AN, with reduced VS activation during the normal weight pictures. This was in comparison to healthy individuals, who showed the opposite pattern (Fladung et al., 2010). In a further study, Fladung et al (2013) found that this VS signal may change over time, in the same way that neural activation evolves over time in substance dependence. In this second study, individuals with AN, whose illness duration was five times shorter than those in the first study, showed the same increased activation to underweight pictures and decreased activation to normal weight pictures in comparison to healthy controls. However, in the AN group the signal did not differ between categories, suggesting that the signal in the VS may evolve over time, as the illness duration increases. The authors suggest that over time cues associated with self-starvation become linked to strong motivational value, which further reinforces starvation and weight-loss behaviour (Fladung et al., 2013). A pronounced bias in attention towards stimuli, and increased positive feelings, have also been associated with physical activity in AN (Giel et al., 2013).

1.10.2 A shift from positive to negative reinforcement?

Selby et al (2013) further suggest that positive emotion/reinforcement may be particularly relevant in the initial stages of AN, with negative reinforcement becoming more important in maintaining behaviour over time, where weight-loss behaviour is used to reduce negative emotions. It may be that the later stages of AN and drug dependence are similar, in that the early rewarding effects of food restriction and drug taking may cause

these behaviours to be repeated and become habitual/compulsive in nature (Zink & Weinberger, 2010). This may be reflected by synaptic changes reported in both substance dependence and AN (Everitt & Robbins, 2005; Fladung et al., 2013).

The synaptic changes seen over time in drug dependence are well studied. The initial DA-dependent reinforcing effect of drugs is associated with a feeling of euphoria, and is experienced as rewarding (Volkow et al., 1996), thus positively reinforcing their use. These DA-dependent effects cause drugs themselves and drug-associated stimuli to gain incentive salience and promote further drug-seeking behaviour (Everitt & Robbins, 2005). The repeated and prolonged DA increase results in synaptic changes in DA pathways, and these changes may be responsible for the formation of compulsive habits in substance dependence (Wolf, 2002). These later stages of habitual drug-seeking and taking may be negatively reinforced by the withdrawal symptoms experienced in absence of the drug, during which individuals can experience both physical and emotional negative states (Koob & Volkow, 2010). Protracted withdrawal is associated with hypofunctioning of the DA pathways and anhedonia (Volkow et al., 2007), which may result in an increased drive for further drug-seeking to counteract this. Avoiding these withdrawal symptoms is likely to play a big role in reinforcing drug use, suggesting that the later stages of compulsive drug use may also involve negative reinforcement.

The complex interplay of positive and negative reinforcement in the development of compulsive behaviour is also emphasised by habit formation studies in OCD. Whilst theories of habit formation in AN and substance dependence have been largely focused on appetitive habits resulting from initially rewarding outcomes, evidence suggests that OCD may be underpinned by the formation of avoidance habits. The compulsions seen in OCD do not seem to develop from an initially rewarding outcome, but rather are typically used to avoid some undesirable consequence (Gillan et al., 2013). These avoidant habits may be

related to increased punishment sensitivity reported in OCD (Fullana et al., 2004), in which patients' compulsions reduce distress, and as such may be experienced as an immediate avoidance of punishment (Salkovskis, 1999). If avoidance is important in the development of OCD, it may also have an impact on habit formation in AN and substance dependence. Individuals with AN have been shown to have both heightened reward and punishment sensitivity, suggested to reflect the avoidant and anxious behaviours seen in AN, which may be used as a means of avoiding increased emotional reactivity to reward and punishment (Jappe et al., 2011). As such, habits in AN may develop as an avoidance of the negative emotions associated with food and weight gain. In contrast, substance dependence is associated with decreased reward and punishment sensitivity (de Ruiter et al., 2009). Whilst compulsive habit behaviours in OCD, appear to begin as the avoidance of something negative, initial drug taking in substance dependence may be much more dependent on increasing the experience of reward. This process is less clear in AN, in which behaviour may begin as the pursuit of something rewarding (weight loss) and/or the avoidance of negative states and anxiety associated with food.

1.10.3 Section Summary

Theories of dependence that suggest a gradual shift from positive to negative reinforcement are comparable to theories that suggest a shift from goal-directed to habitual control of behaviour. In AN, weight-loss behaviour may begin as goal-directed behaviour which is positively reinforced, and once this behaviour is repeated, becomes habitual and increasingly negatively reinforced. The development of habitual compulsive behaviour across disorders may involve a complex balance between both positive and negative reinforcement, and the two do not appear to be mutually exclusive in this context. Although compulsive behaviour may begin as the pursuit of something positive, it may

also be maintained by the avoidance of negative states, further perpetuating the compulsive act.

1.11 The role of starvation in compulsive behaviour

The evidence reviewed so far suggests that compulsive weight-loss behaviours seen in AN may be associated with aberrant neurocircuitry, and dysfunctional mechanisms of learning and reward that promote compulsive behaviour. Crucially, there is evidence that the physiological consequences of starvation promote compulsivity and habit learning, and enhance positive reinforcement.

Behavioural evidence in humans suggesting that starvation is associated with the development of compulsive behaviours derives from the Minnesota Experiment (Keys et al., 1950), in which previously healthy males were restricted to half their average food intake for six months. These individuals developed food rituals and obsessions, some of which persisted after food restriction ceased, and some engaged in binge-eating or excessive exercise. They also experienced cognitive impairment and periods of low mood during the study. These individuals were psychologically and physically healthy prior to the experiment, suggesting that these symptoms were due to the food restriction imposed during the experiment. It is possible that starvation effects impact on aberrant neurocircuitry, and dysfunctional mechanisms of learning and reward, to promote compulsive behaviour in a vicious circle.

In the animal model of AN, Activity Based Anorexia (ABA), compulsive hyperactivity becomes intrinsically linked to food restriction. Rats on a restricted diet given free access to a running wheel will increase activity to the point of death (Adan et al., 2011; Routtenberg & Kuznesof, 1967). Interestingly, young female rats, as in human AN, show particular susceptibility to this effect (Hancock & Grant, 2009). Rat models also show Food Anticipation Activity (FAA), in which an increase in physical activity precedes a meal (Mistlberger, 1994). This increase in activity preceding a meal has also been

documented in AN patients (Scheurink et al., 2010). These phenomena have been suggested to reflect an evolutionary advantage of increased activity (foraging) during times of famine (Illius, Tolkamp, & Yearsley, 2002), and appear to show a link between food restriction and increased physical activity. Evidence from the ABA model also suggests a role for DA and serotonin dysfunction in the development of hyperactivity during food restriction. Antagonism of DA receptors is shown to increase food intake and decrease overall physical activity in ABA rats (Verhagen, Luijendijk, Hillebrand, & Adan, 2009). Similarly, DA depletion and DA receptor blockade in the NAc decreases FAA (Barbano & Cador, 2006; McCullough & Salamone, 1992). Serotonin has a suppressive effect on food intake (Simansky, 1996), and a decrease in food intake is seen in rats treated with serotonergic agonists (Clifton, Lee, & Dourish, 2000; Lee, Kennett, Dourish, & Clifton, 2002). Furthermore, a decrease in 5HT release in the NAc is seen in ABA rats (Verhagen, Luijendijk, Korte-Bouws, Korte, & Adan, 2009). Given that AN is associated with altered DA and serotonin levels (see Section 1.8.2), this evidence suggests that alterations in these neurotransmitters during the chronic food restriction of AN may increase vulnerability to compulsive exercising.

Food restriction has also been linked to an increase in reward sensitivity. Chronic food restriction, resulting in significant body weight loss, has been shown to increase reward effectiveness when electrically stimulating brain reward circuitry in rats (Fulton, Richard, Woodside, & Shizgal, 2004). Moreover, body weight correlates with the stimulation threshold for reward, in that a lower body weight leads to a weaker stimulation threshold (Abrahamsen, Berman, & Carr, 1995). This effect can also be seen in drug reward. Chronic food restriction in rats has been found to enhance the rewarding properties of drugs by up-regulating synaptic plasticity in the NAc (Carr, 2007). This increased sensitivity to reward during food restriction may underpin reports of increased salience and

attention for disorder-related cues in AN (Fladung et al., 2010; Fladung et al., 2013; Giel et al., 2013). Zink et al (2010) suggest that these disorder-related cues gain incentive salience through a molecular cascade in which starvation-induced reductions in glucose and insulin lead to an increase in phasic DA transmission in the VS, a process which conditions associated cues to become highly motivationally salient. This salience increases the likelihood that the behaviour will continue, in the same way as drug associated cues in substance dependence (Zink & Weinberger, 2010). In this way, the neurobiological changes associated with chronic food restriction may enhance the experience of reward in AN, and positively reinforce disorder related compulsions.

The reliance on habits or stimulus-response learning, suggested to lead to compulsive behaviour, may be potentiated in times of stress. Stress is shown to modulate cognitive memory systems in favour of neo-striatum dependent habit systems (Schwabe et al., 2007). Furthermore, participants exposed to an experimental stressor have been shown subsequently to rely on habits during an instrumental learning task, and to show reduced knowledge of the action-outcome associations needed for goal-directed behaviour (Schwabe & Wolf, 2009). Food shortage has also been associated with impairments in memory in animals (Plaçais & Preat, 2013), and even brief food restriction is shown to lead to alterations in gene expression of stress hormones (Guarnieri et al., 2012). Thus in AN, psychological and physical stressors associated with the disorder, as well as chronic food restriction, may promote reliance on habits.

1.12 Compulsivity as a transdiagnostic concept

The core feature that unites AN, OCD and substance dependence is the compulsive nature of disorder-specific behaviour. As discussed so far, neurobiological correlates of compulsive behaviour can be seen across these disorders. Robbins et al (2012) have suggested a transdiagnostic approach to compulsivity, arguing that this behavioural construct has cross-diagnostic significance, as evidenced by commonalities and comorbidities in behaviours across a range of disorders. They posit that a transdiagnostic approach to compulsivity may aid in the development of novel treatment avenues relating to specific behaviours, rather than focusing on diagnosis (Robbins et al., 2012). This focus on constructs of behaviour, as opposed to symptoms and disorder categories, reflects the recent RDoC (Research Doman Criteria) research strategy adopted by the National Institute of Mental Health (NIMH). This strategy emphasises the need to break away from the use of symptoms and diagnostic categories for classification. Instead, research should focus on the variables that define certain dimensions of behaviour, or constructs, seen transdiagnostically across psychiatric disorders (Insel et al., 2010). The RDoC framework suggests researchers should aim to define these constructs in terms of multiple units of analysis (i.e. genes, circuitry, behaviour, self-report and experimental paradigms). Compulsive behaviour is currently included as a behavioural manifestation of 'Habit' in the RDoC framework, in line with the discussion in Section 1.9 that aberrant habit formation may underpin compulsive behaviour.

With this framework in mind, focusing on compulsivity as a transdiagnostic concept may help in understanding commonalities in the compulsive behaviours seen in AN and other disorders, such as OCD and substance dependence. There is a huge unmet need for translational research in AN to develop novel treatments, especially for adults with severe AN. Effective treatments require an optimal understanding of processes

underlying AN, so that the correct treatment targets are identified. The use of a transdiagnostic approach to compulsive weight loss behaviours in AN may begin to address this problem. The aim of this thesis is to explore a transdiagnostic perspective of compulsivity in relation to behaviour in AN, in order to help delineate behavioural and neural underpinnings of persistent weight-loss behaviour in AN.

1.13 Overview of Introduction Part 3: Considerations for Research Design in Anorexia Nervosa

Part 3 will focus on the challenges of research design in AN, taking into account the literature reviewed in Parts 1 and 2. The confounding effect of comorbidities and medication will be discussed and considered in terms of the difficulties in untangling the effects of these variables from those that can be attributed to AN diagnosis. Similarly, the effects of malnutrition as a confounding variable are acknowledged, and the use of individuals recovered from AN in order to avoid malnutrition effects is considered. Finally, subtypes of AN are discussed in light of differences in psychopathology between subtypes, and potentially differing relationships to compulsivity.

1.14 Comorbidities in Anorexia Nervosa

As discussed previously in Section 1.4, individuals with AN often have comorbid diagnoses, which may predate their AN diagnosis, and persist into recovery. In particular, comorbid diagnoses of anxiety and/or mood disorders are often reported. This makes untangling the effects of AN psychopathology, versus the effects of comorbid diagnoses challenging for researchers. Any experimental differences between those with AN and healthy individuals could arguably be the result of the increased levels of anxiety and/or depressive symptoms in these individuals. For example, emotion processing deficits, which are often seen in AN, are also associated with depression (Surguladze et al., 2004), and deficits in emotional processing have been found to attenuate or disappear when controlling for depressive symptoms (Jänsch, Harmer, & Cooper, 2009). Furthermore, comorbid obsessive compulsive symptoms are reportedly a better predictor of facial discrimination accuracy than AN symptoms (Castro, Davies, Hale, Surguladze, & Tchanturia, 2010). Due to high rates of comorbidity in AN, it is extremely challenging to select an experimental group free from comorbid diagnoses, and so measuring and controlling for these confounding variables in research is an important consideration in order to untangle the effects of AN psychopathology from comorbid symptomology.

1.15 Medication Use in Anorexia Nervosa

Individuals with AN are often on antidepressant and/or antipsychotic medication, which poses a further challenge when interpreting differences between these individuals and healthy controls. The sensitivity of experimental tasks to medication status has been reported, for example, altering information processing of emotional stimuli (Harmer, Mackay, Reid, Cowen, & Goodwin, 2006). In a study investigating emotional processing in AN, subtle but significant differences were found between those in the AN group taking

antidepressant medication, and those who were not. For example, those not on medication misclassified anger more often, and those on medication tended to misclassify more faces as fearful (Jänsch et al., 2009). Although these findings were reported as preliminary, with only a small sample size for comparison between those medicated and unmedicated, this emphasises the potential importance of medication status. Furthermore, antidepressant medications are shown to alter the function of brain activity during experimental tasks, and resting neural connectivity (Del-Ben et al., 2005; McCabe & Mishor, 2011; Rose, Simonotto, Spencer, & Ebmeier, 2006; van de Ven, Wingen, Kuypers, Ramaekers, & Formisano, 2013), and so must be taken into account when interpreting this data. To avoid the potential confound of medication status, it is optimal to select an experimental group free from antidepressants/antipsychotics. It is however acknowledged that this is a challenge when considering the high number of both acute and recovered individuals taking these medications, and so controlling for this variable is important during analysis.

1.16 The effects of starvation in Anorexia Nervosa

As discussed in Section 1.11, weight-loss behaviours in AN may be exacerbated by the effects of starvation, in a way that promotes the development compulsions and habits. In addition to the effects of starvation on compulsivity and habit formation, emaciation has more widespread effects on brain function (Kaye et al., 2009). As a result of starvation, individuals with AN show a reduction in grey matter, alterations in white matter, and metabolic and endocrine disturbances (Blasel et al., 2012; Castro-Fornieles et al., 2007; Mainz, Schulte-Ruther, Fink, Herpertz-Dahlmann, & Konrad, 2012; Van den Eynde et al., 2012). Changes in diet and weight have also been shown to alter DA and serotonin metabolism (Avena, Bocarsly, & Hoebel, 2012; Johnson & Kenny, 2010). These aberrancies are likely to blame for lowered mood, deficits in cognitive function, emotional dysregulation, and alterations in hormonal and autonomic systems (Kaye et al., 2009). As

such, these starvation-related effects may underpin behavioural differences to healthy controls in experimental tasks, making it difficult to differentiate state-related and premorbid trait related differences in AN.

1.16.1 State Versus Trait alterations

As discussed above, emaciation may lead to or exacerbate symptoms and behaviour in AN, and presents a challenge for disentangling the cause and effect between pathological eating behaviour in AN, and the impact of malnutrition on behavioural and neural processes (Kaye, Wierenga, Bailer, Simmons, & Bischoff-Grethe, 2013). In addition to state-related alterations that occur as a result of starvation, there also seem to be a number of premorbid vulnerabilities that may contribute to the development of AN. A genetic vulnerability to developing AN has been shown in twin studies (Bulik et al., 2006; Walters & Kendler, 1995), and is further evidenced by the high heritability of disordered eating, preoccupation with weight and body shape, dietary restraint, and binge/purge behaviour (Bulik, Slof-Op't Landt, van Furth, & Sullivan, 2007; Rutherford, McGuffin, Katz, & Murray, 1993; Wade, Martin, & Tiggeman 1998). Certain personality traits such as harm avoidance, perfectionism, inhibition, altered interoceptive awareness, and obsessive-compulsive personality traits have been suggested to predate AN, and persist after recovery (Anderluh et al., 2003; Lilenfeld et al., 2006; Stice, 2002).

Differentiating differences due to state versus trait-related alterations in AN presents a major challenge to researchers. Longitudinal studies are difficult due to the rarity of the disorder, and years of follow up required (Kaye et al., 2009). As an answer to this problem, some researchers have opted to study those recovered from AN, who no longer present with the effects of starvation. The rationale for this being that remaining differences may represent trait-related alterations in those vulnerable to AN, such as the

personality traits that are shown to predate development of AN, and persist after recovery. However, it is important to acknowledge that this is further confounded by the possibility that some differences could potentially represent 'scars' of the illness, resulting from the development of the disorder. In light of these issues, the research reported in this thesis used both individuals with a current diagnosis of AN, and those who have fully recovered.

1.17 How do we define recovery from Anorexia Nervosa?

In order to utilise the advantages of using a sample of individuals recovered from AN, a state of 'recovery' must be defined and operationalised. As pointed out by Walsh (2008) there is a lack of consensus in the ED field as to what defines recovery, which limits comparison of results across research studies (Walsh, 2008). An important issue in the definition of recovery is the length of time for which individuals should be free of symptoms. Studies have varied largely in defining durations for recovery, from eight weeks to three years (Bachner-Melman, Zohar, & Ebstein, 2006; Daley, Jimerson, Heatherton, Metzger, & Wolfe, 2008; Herzog et al., 1999; Kordy et al., 2002; Von Holle et al., 2008), making comparison of results across studies very difficult. Shorter durations for defining recovery may be limited in their representation of long term recovery, as research shows the highest risk for relapse is within 6-17 month post treatment (Carter, Blackmore, Sutandar-Pinnock, & Woodside, 2004). However, longer durations have also been criticised for being less inclusive, and reducing the number of subjects reaching the defined recovery criteria in research studies (Walsh, 2008).

Early definitions of recovery focused mostly on physical symptoms, such as recovery of weight and menstruation (Morgan & Russell, 1975). However, weight restoration alone is not likely to indicate full recovery, as these individuals may continue to display the behavioural and psychological aspects of an ED, and may be more accurately

referred to as ‘weight restored’. The menstrual status criteria for AN is no longer included in the DSM-V (See Section 1.3.1), and has limited efficacy in defining recovery, as it is not applicable to males, females on oral-contraceptives, or post-menopausal women. However, researchers may still include this as an additional component in defining recovery.

The importance of behavioural (Bulik, Sullivan, Fear, & Pickering, 2000; Field et al., 1997; Strober, Freeman, & Morrell, 1997) and psychological (Bachner-Melman et al., 2006; Couturier & Lock, 2006) aspects of recovery have increasingly been recognised. The importance of including these cognitive or psychological components for recovery is emphasised in studies showing that remaining anorexic thoughts and concerns about weight and shape are predictive of relapse (Carter et al., 2004; Federici & Kaplan, 2008). This has been suggested to reflect a deficiency in how recovery is defined in the studies reporting these remaining symptoms (Keel, Dorer, Franko, Jackson, & Herzog, 2005). When psychological recovery is included, individuals appear comparable to controls on body dissatisfaction, negative affect, disordered eating, drive for thinness and endorsement of the thin ideal (Bachner-Melman et al., 2006; Cogley & Keel, 2003). Furthermore, subjective sense of recovery is reported not to differ between those with and without psychological recovery from an ED, with both groups considering themselves fully recovered (Bardone-Cone, 2012). This suggests that the psychological component must be assessed objectively, as individuals themselves may not recognise their stage of recovery. Psychological recovery is often determined by the use of the EDE (Fairburn, Cooper, & O'Connor, 2008), or EDE-Q (Fairburn & Beglin, 2008), which assess behavioural and psychological aspects of eating disorder symptoms, however these focus only on the past 28 days, and so assessment of long-term recovery is limited.

The presence of residual comorbid non-ED related psychopathology after recovery is also an important issue in defining recovery, as elevated levels of anxiety, depression and obsessive-compulsive symptoms may remain. Including individuals with clinical or sub-clinical levels of non-ED psychiatric symptoms may lead to difficulties in untangling results in terms of the effects of these symptoms, versus the effects of a previous ED diagnosis. However, if these represent trait markers of vulnerability to developing AN, excluding individuals with other psychiatric symptoms may not be representative of recovery, and may be detrimental to recruitment.

Bardone-Cone et al (2010) outlined a set of proposed criteria for recovery in an attempt to operationalise a definition of recovery for use in research (Bardone-Cone et al., 2010). They suggest that individuals fully recovered from an ED should be indistinguishable from healthy controls, in indices of weight, behavioural and psychological aspect of ED symptoms. They propose the following criteria for recovery:

1. Individuals no longer meet the diagnostic criteria for an ED.
2. No binge/purge or fasting behaviours have been displayed in the past 3 months.
3. Current BMI is above 18.5kg/m².
4. Individuals score within 1SD of the community norms on the EDE-Q subscales.

They suggest that the absence of the forth criterion equates to 'partial recovery', i.e. the absence of psychological recovery. These criteria were utilised in a study comparing fully recovered, partially recovered and healthy controls on measures of ED symptoms, psychosocial functioning, and other Axis I psychopathology. The fully recovered group were found to be indistinguishable from the control group on all measures, although they had elevated levels of current anxiety disorders (Bardone-Cone et al., 2010). Based on

these results, this thesis aims to use similar stringent criteria to define a recovered group for comparison to individuals with current AN, and healthy controls.

1.18 Subtypes of Anorexia Nervosa

Individuals with restrictive-type AN lose weight solely through restricting their food intake, whilst 50% of individuals with AN will also develop purge and/or binge behaviours, more akin to the binge/purge behaviours seen in BN (Eddy et al., 2002). Many studies in AN do not differentiate between these subtypes (for subtype criteria see Section 1.3.1), despite evidence of important psychopathological and neurological differences observed between these subtypes. Both subtypes are associated with excessive perfectionism (Fassino et al., 2006), cognitive rigidity and deficits in set shifting (Friederich & Herzog, 2011), as well as ruminations and obsessions with food, weight and shape (Fairburn & Harrison, 2003). However, it has been suggested that these subtypes can be differentiated by their oppositional impulse control modulation (Brooks, Rask-Andersen, Benedict, & Schiöth, 2012). Individuals with restricting-type AN exhibit extremes of self control, particularly in their denial of food despite starvation, and tend to be overly concerned by consequences (Kaye, Wierenga, Bailer, Simmons, Wagner, et al., 2013). This is evidenced in their ability to delay reward (Steinglass, Figner, et al., 2012), which likely helps in the maintenance of persistent food restriction. In contrast, individuals with binge/purge AN and BN, tend to have poor impulse control, and show greater novelty seeking, and less concern over future consequences (Cassin & von Ranson, 2005; Lilenfeld et al., 2006; Marsh et al., 2009; Wagner et al., 2006).

In terms of the neurobiological differences between those with and without binge/purge symptoms, differences in striatal DA function have been reported. Restrictive-type AN is associated with increased anterior VS binding of DA receptors and increased

CSF HVA levels of DA, whereas individuals with binge/purge type AN and individuals recovered from BN show normal DA receptor binding and CSF HVA levels (Bailer et al., 2013; Kaye, Frank, & McConaha, 1999). FMRI studies of task-induced brain activity have largely focused on differentiating AN and BN, rather than by AN subtype. These have shown altered activity in cognitive control circuits, consistent with enhanced inhibitory control in AN, and impaired inhibition in BN. This may reflect the extreme self-control, and ability to persist in restriction in AN, which is driven by exaggerated dorsal cognitive control circuit function. In contrast diminished activity in these circuits in BN is reflected by an inability to self-regulate and control the impulse to overeat (Kaye, Wierenga, Bailer, Simmons, Wagner, et al., 2013). In addition, when compared with AN, those with BN have been shown to have increased activation in reward regions in response to food stimuli, which may impinge further on cognitive control (Brooks, O′Daly, et al., 2011). Preliminary evidence of increased activation in cognitive control regions has also been reported in restrictive compared to binge/purge AN (Brooks, O'Daly, et al., 2012). It is plausible that those with binge/purge symptoms in AN may have differential activation in cognitive control and reward circuits as reported in BN, which may drive their inability to persist in self starvation.

The differences seen between the subtypes of AN are also important in the context of compulsivity, which is the focus of this thesis. Compulsivity is sometimes confused with impulsivity, which is defined as the tendency to perform actions prematurely without foresight (Dalley et al., 2011). In those with EDs, the presence of binge-purge behaviours appears to be associated with higher levels of impulsivity compared to those with ‘pure’ restricting-type AN (Claes, Vandereycken, & Vertommen, 2005; Favaro et al., 2005; Rosval et al., 2006; Waxman, 2009). This may explain higher levels of comorbidity between EDs characterised by binge-purge behaviours and addictions (O'Brien & Vincent,

2003), discussed in Section 1.7.1. One hypothesis is that individuals higher in impulsivity may be less able to sustain starvation, instead acting on the body's demand for food. This contributes to binge-purge behaviours, which can subsequently take on a compulsive quality with repeated engagement. In contrast, pure restriction may be more shaped by increased response inhibition from the outset, leading to engagement in persistent restriction behaviours, which may also subsequently become compulsive with repetition. The presence of impulsivity, or a lack of impulse control, may therefore contribute to the specific presentation of eating disorder.

In light of the differences in impulse control evident between subtypes, this thesis will differentiate between subtypes in the analysis and interpretation of results. In Chapter 2, both subtypes were included in order to qualitatively explore the subjective experience of compulsivity across behaviours in AN. Similarly, Chapter 3 includes both subtypes of AN in the validation of two new measures of compulsive weight-loss behaviour. The differences between subtypes were explored by including and subsequently excluding those who reported binge/purge symptoms in the analyses. However, it was decided that for the behavioural and neural investigation of compulsivity in AN reported in Chapters 4 and 5, only individuals with restrictive-type AN would be included. This was decided in light of the differences reported above regarding behavioural differences in impulse control, and neural differences between subtypes. Moreover the limited sample size of the studies which would not allow for effective comparison between subtypes. Restrictive-type AN participants were used in line with the hypothesis that elements of impulsivity and compulsivity likely contribute to binge/purge behaviours, whilst purely restrictive behaviour appears to be more driven by compulsivity alone.

2. Compulsive behaviour in Anorexia Nervosa: A Qualitative Investigation.

2.1 Overview

As identified in Chapter 1, the compulsive and driven nature of weight-loss behaviour in AN is a central characteristic of the disorder. This compulsive nature appears to parallel the characteristic behaviours of other compulsive disorders, such as OCD and substance dependence, and these parallels are not only be seen at the symptom level, but also at a behavioural and neural level. Despite these similarities, little research has focused on compulsivity in AN, and its potential transdiagnostic significance. As an initial stepping stone, this chapter therefore aims to investigate the subjective experience of compulsive weight loss behaviour in AN, and the validity of increasing suggestion of parallels with substance dependence.

2.2 Background

In Section 1.7.1 the comparison between compulsive weight-loss behaviours in AN and the compulsive drug-seeking behaviour inherent in substance dependence was explored. The drug-seeking behaviour of addicts may parallel the relentlessness with which individuals with AN pursue weight loss. Food restriction and subsequent weight loss is often experienced as initially rewarding and pleasurable in those with AN (Park et al., 2011, 2012; Scheurink et al., 2010), but individuals find it increasingly difficult refraining from weight loss behaviour despite adverse consequences. As discussed in Section 1.8.1 behavioural and neurobiological similarities are also evident between the two disorders. Both disorders are associated with deficits in tasks that tap cognitive flexibility (Bühren et al., 2012; Hildebrandt et al., 2015; Holliday et al., 2005; Izquierdo & Jentsch, 2012; Saraswat et al., 2006; Sarrar et al., 2011; Steinglass et al., 2006), which is defined as a rigid cognitive style, and suggested to contribute to compulsivity (Fineberg et al., 2010). Furthermore, dysfunction in the cortico-striatal circuitry suggested to underpin compulsivity (Fineberg et al., 2010; Robbins, 2007), can also be seen in AN and substance dependence (Everitt & Robbins, 2005; Fladung et al., 2013; Rothemund et al., 2011).

Binge-eating behaviour or 'food addiction', in contrast to restrictive behaviours, has also received increasing attention. Similarities between the compulsive behaviours seen in substance addiction and BED, such as diminished control over consumption and continued excessive consumption despite negative consequences, have led to suggestions they may be underpinned by similar processes (Corwin & Grigson, 2009; Davis & Carter, 2009). This may also be relevant for binge/purge type AN, which involves repeated episodes of binge-eating, and may also share this compulsive nature. Indeed, a recent study found that a shared propensity toward relying on previously learned habits rather than

goal-directed action choice was evident in substance dependence and binge-eating behaviour in obese subjects (Voon et al., 2014). This suggests a commonality in the persistence of maladaptive behaviours across these psychiatric disorders may by underpinned by aberrancies in similar behavioural processes. The possibility of a disrupted balance between the goal-directed and habit-based systems as the mechanism behind maladaptive persistent behaviours across compulsive disorders was discussed in Section 1.9.

Despite increasing interest in the transdiagnostic relevance of compulsive behaviour across psychiatric disorders, and recent suggestions implicating well entrenched compulsive weight-loss behaviours in the persistence of behaviour in AN (Walsh, 2013), there is a paucity of research investigating the compulsive nature of behaviour in AN, and suggested parallels with other disorders. A better understanding of the behavioural parallels between AN and substance dependence may guide further research investigating the underlying mechanisms of behaviour, and ultimately aid the development of novel treatment strategies targeting these behaviours. With this in mind, the study reported in this chapter aimed to examine the validity of the suggested parallels between AN and substance addiction with a qualitative investigation of the subjective experience of compulsive weight-loss behaviour in AN.

2.3 Aims

- To use a qualitative analysis to investigate how compulsive weight-loss behaviour is experienced by individuals currently suffering from AN.
- To investigate parallels in the compulsive weight-loss behaviour seen in AN and the criteria for Substance Use Disorders (SUDs)

2.4 Hypotheses

- The compulsive nature of weight-loss behaviour will be viewed by participants as playing a central role in the persistence and maintenance of AN.
- An overlap will be seen between the qualitative themes that emerge from this study and the DSM-V criteria for SUDs.

2.5 Methods

2.5.1 Participants

Forty participants between the ages of 18-65 were recruited for a group of individuals currently suffering from AN. Participants were recruited via email, internet and poster advertisement. This included advertisement on the BEAT website. Additionally, a number of participants were recruited from the Oxford Research List for Anorexia Nervosa (ORLA) of individuals with experience of AN, maintained by the research team at the University of Oxford. Participants in this study were recruited as part of a larger questionnaire study carried out by our research group (See Chapter 3). The study was described to potential participants as an investigation of two new measures of compulsive behaviour in AN, and the concept of compulsive behaviour in AN was described to participants in the information sheet (See Appendix 2.2). Participants were recruited on the basis of a self-reported diagnosis of AN from a healthcare professional, and a self-reported current BMI of below 18.5.

2.5.2 Study Procedure

The research protocol was reviewed and approved by the NRES Committee South Central – Berkshire B (Ref: 13/SC/1370; see Appendix 2.1). Data was collected using the Bristol Online Survey system (BOS; Institute of Learning and Research Technology, University of Bristol, UK). Participants were initially sent an information sheet and asked some screening questions via email to ensure eligibility for the study. Participants were then provided a link to an online consent form (see Appendix 2.3), and their responses to a number of questions were recorded online. Participants completed the Eating Disorder Examination-Questionnaire (EDE-Q; described below) and Clinical Impairment Assessment (CIA; described below) to measure ED symptoms, followed by demographic

questions. They were then provided with a number of prompt questions and space to comment on the compulsive nature of behaviour in AN. Data was stored automatically and downloaded from the online programme for analysis. Participants were compensated with a £5 Amazon voucher upon completion of the study.

2.5.3 Measures

Eating Disorder Examination Questionnaire (EDE-Q): The EDE-Q (Fairburn & Beglin, 2008) is a 28-item self-report questionnaire (see Appendix 2.4). It is comprised of four subscales: eating concerns, weight concerns, shape concerns, and restraint. It also provides a global score which was used in this study as a measure of eating disorder symptoms. This questionnaire asks participants to focus on the past 28 days when answering questions and uses a 7 point scale in which higher scores indicate greater symptoms. The questionnaire has been shown to have good reliability and validity (Fairburn & Beglin, 2008), as well as acceptable internal consistency and test-retest reliability (Luce & Crowther, 1999).

Clinical Impairment Assessment (CIA): The CIA (Bohn & Fairburn, 2008) is a 16-item self-report measure used to assess the severity of psychosocial impairment caused by eating disorder psychopathology (see Appendix 2.5). It asks participants to focus on the past 28 days and rate how much each statement has applied to them in this period. The CIA has been shown to have high levels of internal consistency, construct and discriminant validity, test-retest reliability and sensitivity to change (Bohn & Fairburn, 2008).

Compulsivity Questions: Participants were asked to reflect on their experience of compulsive behaviour in AN, and their responses were recorded online. There was no space or time limitation and participants could write as much or as little as they felt was

appropriate. Participants read the following information and questions as prompts for their responses:

We are interested in any comments or reflections you may have about the compulsive and driven nature of behaviour in anorexia (e.g. excessive exercise and food restriction) and your experience of this.

Please fill in the box below with any comments you have on the following:

1. *What is your experience of compulsion in anorexia- how does it feel?*
2. *How troubled do you feel by compulsive behaviours - and what is most troubling?*
3. *How important do you think the compulsive nature of behaviour is the course of anorexia - its development and/or recovery?*
4. *How do you feel when you are prevented from engaging in any compulsive behaviours?*
5. *Does anything help reduce your sense of compulsion, and/ or the compulsive behaviours that trouble you?*
6. *Any other comments.*

Demographic Information: Participants also provided the following demographic information:

- Age
- Age of onset of anorexia nervosa
- Duration of eating disorder
- Type(s) of treatment received (e.g. inpatient, outpatient, day patient),
- Lowest BMI (or height and weight if unknown)
- Current BMI (or height and weight if unknown)

2.5.4 Qualitative Analysis

Responses were downloaded from BOS and analysed using Thematic Analysis (TA) techniques (Braun & Clarke, 2006). A deductive coding method was employed, guided by previous theory and the hypotheses outlined in the current study, whilst allowing for novel themes to arise from the data. Coding and analysis was carried out by hand.

Based on the guidelines for using TA outlined by Braun and Clarke (2006), transcripts were initially read and reread a number of times to facilitate familiarisation with the data set. Initial codes were generated manually by hand by noting key words/phrases of interest in the margin of the transcripts, and the entire data set was systematically coded. These initial codes were then compared and sorted into themes, grouping similar codes together under one broader theme (see Appendix 2.6 for an example this). The content of the themes were reviewed in order to develop appropriate titles. A thematic map was then created in order to visualise and explore the relationships between themes. The themes were then refined into a number of main and sub themes. Finally, the thematic map was reviewed in relation to the entire data set, and themes were further refined in order to best reflect the data as a whole (See Figure 2.1).

To ensure the inter-rater reliability of the coding system, the transcripts were coded again by a second researcher, using the final coding scheme (see Appendix 2.7). The independent researcher was a post-doctoral research assistant in the research team who had experience of working with EDs, but was unfamiliar with the specific hypotheses of the current study. The independent researcher coded 10 of the 40 excerpts, and inter-rater reliability was assessed by comparing the codes given by the independent reader to the original coded data set. This resulted in 89% agreement between researchers in application of the final coding scheme. The independent researcher felt the final coding scheme was an

accurate reflection of the data; however discussion of discrepancies in coding between researchers led to further revision of the final data coding. Following this inter-rater reliability check, the final interpretation of the data and conclusions drawn were discussed with the research team.

The final themes were then assessed for parallels with the DSM-V diagnostic criteria for SUDs (See Figure 2.2) in line with the predictions of the study. These criteria are grouped into four themes as shown in Figure 2.2, assessing impaired control, social impairment, risky use of the substance, and pharmacological criteria.

Figure 2.1 Thematic map showing the themes and sub themes that emerged from the data

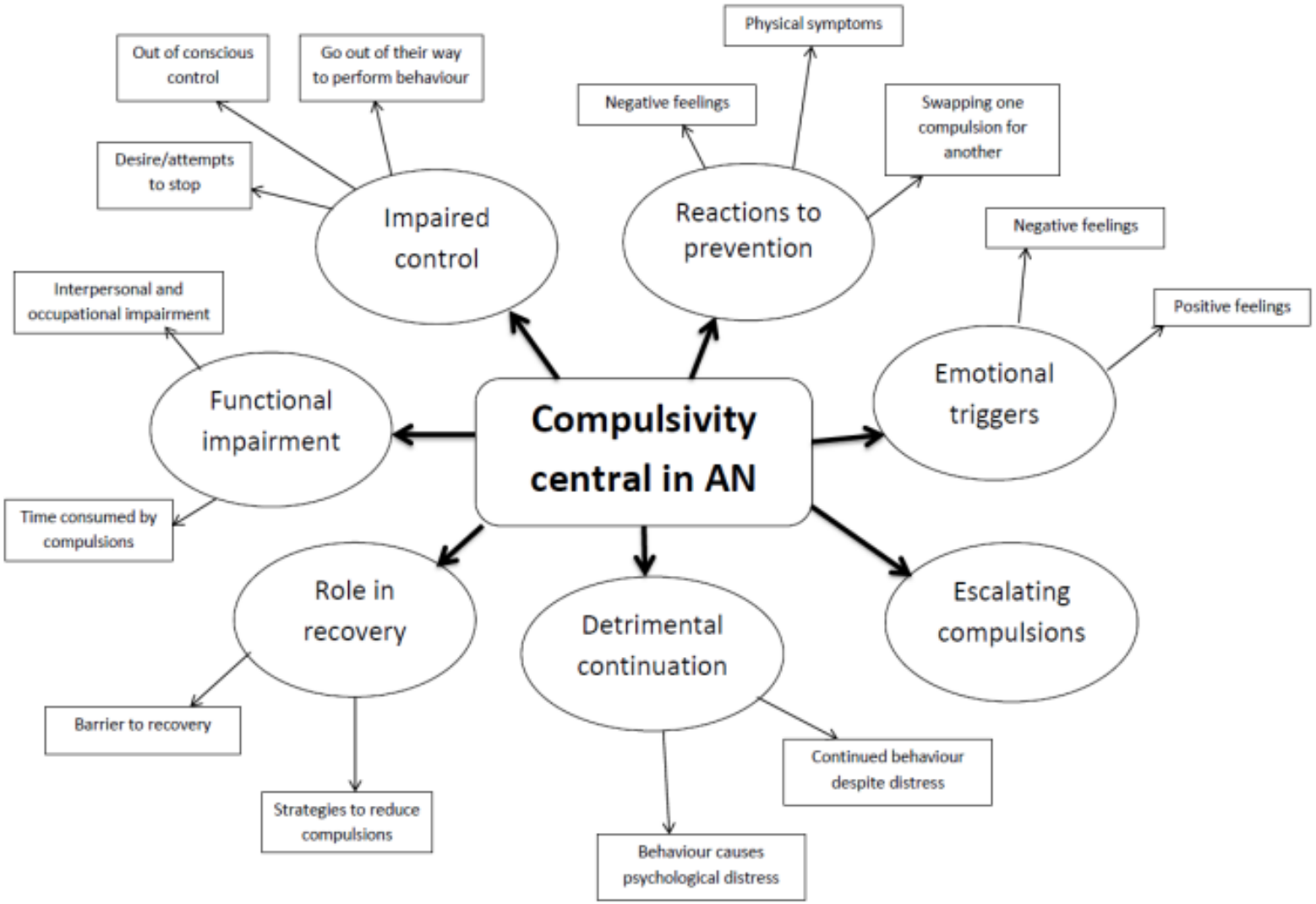
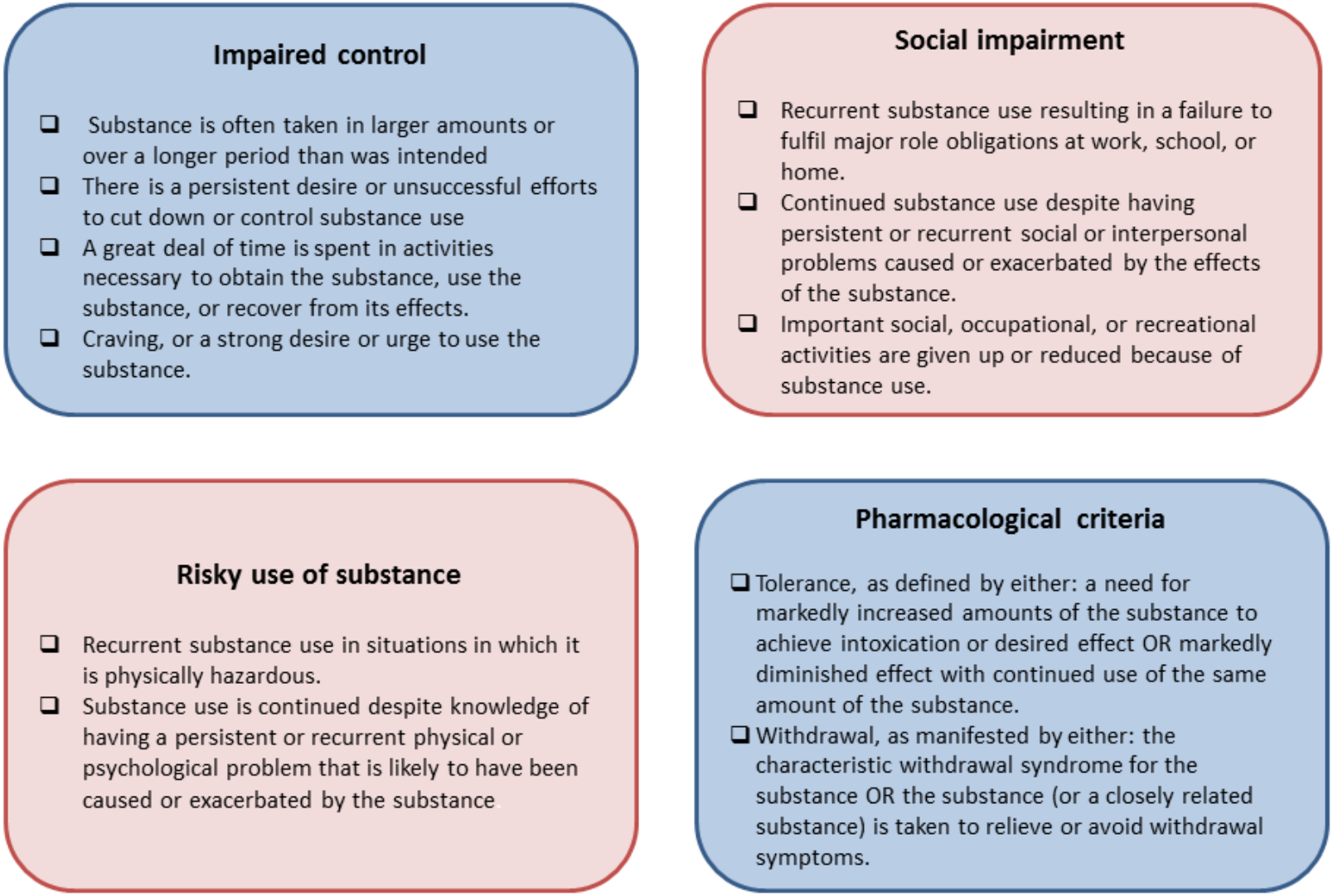


Figure 2.2 The four groups of the DSM-V diagnostic criteria for Substance Use Disorders.



2.6 Results

2.6.1 Demographic results

Forty participants reporting a current diagnosis of AN completed the online questionnaire. Of these forty participants, thirty-nine were female, and one was male. Twenty-two of the participants had received inpatient treatment at least once, twelve had received day patient treatment, and thirty-five had received treatment as an outpatient. Table 2.1 shows mean scores and range of scores on measures of ED psychopathology (EDE-Q and CIA), age, age of onset of AN, length of AN, current BMI and lowest BMI for all participants. Fifteen participants reported binge and/or purge symptoms in the past 28 days (four reported binge and purge symptoms, three reported binge symptoms only, eight reported purge symptoms only).

Table 2.1. Demographic and Psychological characteristics

	Mean	***Range***
EDE-Q	4.06	1.09-5.85
CIA	33.35	7-48
Age	28.0	18-60
Age of Onset	16.5	13-27
Length of AN (years)	11.5	1-43
Current BMI	15.9	13.3-18.5
Lowest BMI	13.4	10-15.8

Note: EDE-Q = Eating Disorder Examination Questionnaire; CIA = Clinical Impairment Assessment; BMI = Body Mass Index

2.6.2 Qualitative results

The average number of words per participant was 192, although the variance between participants was great (minimum: 24, maximum: 1405). Using the final coding system resulted in 78.8% of the data set being coded. Eight main themes were identified, within which 14 sub-themes were included, as shown in Table 2.2. The endorsement rate for each main and sub theme is also shown in Table 2.2. Each theme and sub-theme is presented below with verbatim excerpts.

Table 2.2 Themes extracted from a thematic qualitative analysis

Theme	Sub-Themes	Endorsement Rates
1. Compulsivity is central to AN		15/40 (37.5%)
2. Impaired control		25/40 (62.5%)
	2.1 Out of conscious control	25/40 (62.5%)
	2.2 Go out of their way to perform behaviour	5/40 (12.5%)
	2. 3 Desire/attempts to stop	12/40 (30%)
3. Functional impairment		15/40 (37.5%)
	3.1 Time consumed by compulsions	8/40 (20%)
	3.2 Interpersonal and occupational impairment	11/40 (27.5%)
4. Detrimental continuation		18/40 (45%)
	4. 1 Continued behaviour despite insight	11/40 (27.5%)
	4.2 Behaviour causes psychological distress	16/40 (40%)
5. Escalating compulsions		14/40 (35%)
6. Reactions to prevention		29/40 (72.5%)
	6.1 Negative feelings	29/40 (72.5%)
	6.2 Physical feelings	9/40 (22.5%)
	6.3 Swapping one compulsion for another	5/40 (12.5%)
7. Emotional triggers		16//40 (40%)
	7.1 Negative feelings	13/40 (32.5%)
	7.2 Positive feelings	7/40 (17.5%)
8. Role in recovery		26/40 (65%)
	8.1 Compulsivity as a barrier to recovery	21/40 (52.5%)
	8.2 Strategies to reduce compulsions	20/40 (50%)

Theme 1: Compulsivity is central to AN

As the prompt questions in this study lead participants to base their answers around the compulsive nature of behaviour in AN, and due to the deductive nature of the analysis, compulsivity emerged as a central theme from the data. This theme demonstrated that some participants view the compulsive nature of weight-loss behaviour as a central phenomenon in AN, and as key in both the development and maintenance of weight-loss behaviour in AN. This was reflected in participants' feeling that this behaviour characterised AN, and how they would not be 'anorexic' without it.

> *"The compulsive nature of behaviour in eating disorders is what characterises them... if restriction/exercise weren't compulsive, anorexia would be easy to overcome because it would be a conscious choice to 'switch off' the thoughts and stop the behaviours. The problem is that behaviours become compulsive and so it becomes more difficult to not engage in them"* [Participant 31, age 21, 2 year duration of AN]

Theme 2: Impaired Control

The second theme emphasised the lack of control participants felt they had over their anorexic behaviours.

Sub-theme 2.1: Out of conscious control

Participants often described feeling as though their behaviour was out of their control, and felt as though they were controlled or trapped by their disorder.

> *"Compulsion is like a tidal wave- it has so much force it just knocks you over and it is near impossible to push it out of the way and then it consumes you completely. I get scared by how much it controls me."* [Participant 27, age 22, 11 year duration of AN]

Participants spoke of their disorder-related compulsions as being separate from themselves, and often referred to AN as a 'voice' or separate entity driving them to perform these behaviours.

> *"The Eating Disorder (ED) has rules for food, exercise, and life in general. The compulsive part comes in when ED says you MUST restrict, over exercise, weigh a certain amount, wear a certain size, have certain body proportions, etc., and he promises that this will make you perfect, happy, and loved…. In recovery I am troubled by the compulsive nature of his voice and his rules"* [Participant 38, age 36, 23 year duration of AN]

A comparison to addiction was also made by some participants, describing the nature of AN as analogous to an individual feeling controlled by a substance addiction.

> *"It is the way it starts as a need, a compulsion to lose weight or gain control, then the habits you develop to fulfill that become ingrained and the compulsion is no longer owned by you, you become addicted and sticking to your rules is the most important thing. It also makes recovery hard because trying to ignore the compulsions you feel is like trying to get a heroin addict to turn down heroin- near on impossible."* [Participant 27, age 22, 11 year duration of AN]

Sub-theme 2.2: Go out of their way to perform compulsions

Participants described the need to overcome any obstacles in order to perform their compulsive behaviours, and being prepared to do anything to avoid being prevented from them.

> *"I will do anything to make sure that I am not prevented from completing compulsions - I try not to lie in my everyday life, but will often lie about things so that I can engage in compulsive behaviours."* [Participant 31, age 21, 2 year duration of AN]

Sub-theme 2.3: Desire/attempts to stop

Participants emphasised that they did not always want to perform their compulsions, but felt unable to stop or control these behaviours.

> *"I feel troubled a lot and the need to do things everyday that you don't necessarily want to do is the most troubling thing - because I end up missing out on life."* [Participant 29, age 20, 5 year duration of AN]

Unsuccessful attempts at stopping these compulsive behaviours and at recovery in general were described, and participants also commented on their knowledge that any attempts to stop these behaviours would be unsuccessful.

> *"I can set out with the best will in the world to try and eat more or be positive, but the slightest thing can trigger the compulsion in me and then I can't hold onto that positivity. It feels as though I'm not in control of my own life - of what I want to do…."* [Participant 37, age 21, 5 year duration of AN]

Theme 3: Functional impairment

The third theme emphasises the functional impairment participants describe as a result of their compulsive behaviours.

Sub-theme 3.1: Time consumed by compulsions

Participants described the time consuming nature of their compulsions, emphasising that much of their time was taken up by these compulsions, or related thoughts, and the detrimental effect this had on their life.

> *"It consumes every waking minute of my everyday life, controlling what I can and cannot do socially & professionally, what can and cannot eat... I am most troubled by my…. inability to focus on anything else but what I have eaten/will eat"* [Participant 20, age 18, 4 year duration of AN]

Sub-theme 7.2: Interpersonal and occupational impairment

Worsening family relationships were described by participants as a result of AN. This was both due to a reduction in time spent with family due to time consuming compulsions, and worry caused to family members as a result of the participants poor health.

> *"Not allowing my family to see me eat has caused the most problems as it has affected dynamics in the house and my relationship with family has worsened."* [Participant 5, age 18, 1 year duration of AN]

Participants often commented on the all-consuming nature of AN causing problems in both their social and occupational life.

> *"These compulsions lead to isolation, an inability to socialise, trouble working and problems functioning at all in normal day to day life"* [Participant 10, age 34, 7 year duration of AN]

Theme 4: Detrimental continuation of behaviour

The fourth theme focuses on the continued engagement in compulsive behaviour despite acknowledgment that it is detrimental to physical and psychological health.

Sub-theme 4.1: Continued behaviour despite insight

Participants often described feeling distressed by the driven nature of their behaviour, whilst feeling unable to stop engaging in it. Some participants also commented on the irrationality of their behaviour, and felt unable to explain the reasoning behind them.

> *"It's terrible. Feeling like you HAVE to do something and not being able to come up with a realistic, safe, sane, rational reason for it, and knowing that it takes priority over every other aspect of your life."* [Participant 21, age 19, 6 year duration of AN]

Sub-theme 4.2: Behaviour causes psychological distress

Many of the participants describe feeling distressed or troubled by the compulsive nature of AN, and awareness that these continued behaviours are the reason behind this distress.

> *"Above all else, however, compulsions are what make me feel terrible about myself. They make me feel weak and a failure for not being better able to handle their demands, but also weak and a failure for having them in the first place. The need to be constantly doing something/not doing something means that I am basically in a state of dread, fear, and anxiety 24/7."* [Participant 39, age 22, 7 year duration of AN]

Theme 5: Escalating compulsions

Theme five describes the way in which a number of participants felt that their compulsions had increased over time. Some participants referred to a 'snowball' effect of compulsions in AN, as though the compulsive behaviour becomes more extreme over time as they are engaged in repeatedly, with weight loss targets/calorie rules increasing.

> *"The compulsion to restrict more and lose weight used to be the biggest factor in my illness: every day/week I would try to stick to an ever-decreasing calorie limit and get my weight down to a new low."* [Participant 35, age 36, 20 year duration of AN]

An increase in compulsions was associated with increasing weight loss, suggesting that the more weight lost, the stronger the compulsion became to engage in further weight-loss behaviour, and also in other compulsive behaviours.

> *"My experience of the compulsion in anorexia is that it grows as you lose weight. At first, restricting and exercising felt more of a choice than a compulsion but, as I lost more and more weight, restricting became more compulsive, and I would listen to the anorexia instead of trying to make my own mind up"* [Participant 31, age 21, 2 year duration of AN]

A spread of compulsive behaviour beyond disorder-related compulsions was also described by some participants; this included a compulsive attitude towards work, money, and compulsions regarding order and routine.

> *"I am also compulsive about academic work-I work extremely long hours on my studies, almost all hours of the day, and I get the same anxiety/feelings of failure when I don't work all the time."* [Participant 40, age 23, 4 year duration of AN]

Theme 6: Reactions to prevention

Theme six describes participants' reactions to being prevented from engaging in compulsive weight-loss behaviours.

Sub-theme 6.1: Negative feelings

The majority of participants described a very strong negative reaction to being prevented from engaging in compulsive weight loss behaviour, feelings of anxiety were common.

> *"I feel very tense and anxious when I can't engage in a compulsive behaviour. It feels very overwhelming. Like there's something bubbling up inside you and you'll just explode if you can't do the behaviour to release all the tension."* [Participant 37, age 21, 5 year duration of AN]

Participants also often described feeling scared and unsafe when unable to engage in these behaviours.

> *"But if I don't do those things, I simply feel desperately unsafe, lazy, undisciplined and thoroughly bad about myself…. Hell on earth. Intolerable. Desperately unsafe. Sub-human. It simply doesn't bear thinking about."* [Participant 9, age 44, 24 year duration of AN]

Sub-theme 6.2: Physical symptoms

A physical reaction to being unable to carry out compulsions was also described by some participants, with feelings of agitation and restlessness described, but also some more serious physiological symptoms.

> "When I have to increase my portion sizes I get very panicky, sometimes with physiological symptoms like tachycardia, autonomic response etc." [Participant 40, age 23, 4 year duration of AN]

Sub-theme 6.3: Swapping one compulsion for another

Some participants described feeling an increase in the urge to perform a different weight loss compulsion to avoid the anxiety felt when one type of weight loss behaviour is prevented.

> *"I can reduce the difficulty I have with exercise compulsions by restricting my food intake (and reducing the anxiety from food compulsions by increasing my amount of exercise)."* [Participant 31, age 21, 2 year duration of AN]

Theme 7: Emotional triggers

The seventh theme focuses on the triggers or incentives described by participants for compulsive weight-loss behaviours.

Sub-theme 7.1: Negative feelings

Participants often described negative feelings, such as anxiety and fear of fatness, as a trigger for compulsive weight-loss behaviour.

> *"To me it mostly feels as though in order to deal with life, both in terms of practicalities and emotions, the compulsion to not eat or restrict is a way for me to find a way of coping…. It is sometimes hard to see in the moment but it is certainly true that periods of greater stress and anxiety distinctly impact on my eating habits"* [Participant 2, age 26, 12 year duration of AN]

A feeling of being unworthy of food was also described by some participants.

> *"It's not quite as simple as 'not deserving to eat', but I suppose that's what it boils down to, and the compulsions I feel are a huge contributing factor to that governing belief."* [Participant 39, age 22, 7 year duration of AN]

Participants also described feelings of low self-esteem, and its link to the development of compulsions in AN.

> *"I detest being this thin and judge myself accordingly, but there is an undeniable causal link between thinking very little of yourself and caring enough to get better."* [Participant 39, age 22, 7 year duration of AN]

Sub-theme 7.2: Positive feelings

Participants also described the positive feelings associated with engaging in their compulsions. This often centred on feelings of safety, and a sense achievement and success from these behaviours.

> *"The compulsions are frustrating at times, but also comforting and increase feelings of safety."* [Participant 19, age 26, 8 year duration of AN]

A feeling of being in control was also described by participants.

> *"I feel stronger when I control my food and exercise. I have the feeling that I control something and it makes me feel better and less stressed."* [Participant 12, age 25, 8 year duration of AN]

Theme 8: Role in recovery

Theme eight focuses on the role compulsive behaviour has in recovery from AN.

Sub-theme 8.1: Compulsivity as a barrier to recovery

Most participants described their compulsions as the main barrier they face in recovery, suggesting that recovery was dependent on breaking these behaviours. Participants often emphasised their desire to recover, but felt unable to stop or ignore the compulsion to continue their behaviour.

> *"I believe that freeing myself from these compulsions will ease recovery but I struggle to comprehend life without some of my tendencies."* [Participant 5, age 18, 1 year duration of AN]

Participants also commented on the need to intervene with these behaviours early before they become engrained, at which point recovery and breaking these behaviours becomes very difficult.

> *"Compulsions should be caught early before they solidify into 'behaviours'. Need to be challenged in order to recover/manage"* [Participant 13, age 21, 7.5 year duration of AN]

Sub-theme 8.2: Strategies to reduce compulsions

Due to the nature of the prompt questions, participants described a number of ways in which they tried or were able to reduce their compulsions, although many also emphasised this was very often unsuccessful.

> *"I think doing things and talking to people helps reduce compulsion"* [Participant 11, age 18, 2 year duration of AN]

Some participants also suggested that support from others and having someone to talk to was helpful in reducing compulsions.

> *"Support from close family helps to some extent to reduce."* [Participant 17, age 39, 18 year duration of AN]

A few participants also commented on the usefulness of mindfulness techniques, particularly in reducing the obsessional thoughts associated with their compulsions.

> "To reduce my sense of compulsion, I have been able to use mindfulness based techniques to recognise when such irrational thoughts come to mind." [Participant 24, age 21, 7 year duration of AN]

2.6.3 Parallels with criteria for SUDs

The eight main themes that emerged from the thematic analysis were further examined for parallels with the four groups of the DSM-V criteria for SUDs. Six of these main themes appeared to map onto these four groups of criteria, as shown in Table 2.3.

Table 2.3. Qualitative themes mapped on to the four groups of diagnostic criteria for SUDs.

Diagnostic criteria for SUDs	Corresponding themes
Impaired control	Theme 2: Impaired control
	Theme 5: Escalating compulsions
Social impairment	Theme 3: Functional impairment
Risky use of substance	Theme 4: Detrimental continuation
Pharmacological criteria	Theme 5: Escalating compulsions
	Theme 6: Reactions to prevention
	Theme 7: Emotional triggers

2.7 Summary of results

- Eight main themes emerged from thematic qualitative analysis; compulsivity as central to AN, impaired control, functional impairment, detrimental continuation, escalating compulsions, reactions to prevention, emotional triggers, and role in recovery.
- Participants view the compulsive nature of weight-loss behaviour as a central phenomenon in AN, key in the persistence and maintenance of behaviour in AN, and as a major barrier to recovery.
- Emotional triggers and negative reactions to prevention from carrying out behaviours were important maintaining factors of compulsive weight-loss behaviour, and participants felt that this behaviour was no longer under their control.
- Continuation of compulsive weight-loss behaviour was described despite acknowledgment of adverse consequences, and functional impairment.
- The themes that emerged from the qualitative analysis mapped onto the four categories of the criteria for SUDs.

2.8 Discussion

The aim of this study was to employ qualitative methods to explore the subjective experience of compulsive weight-loss behaviour in AN, and examine the validity of the suggested parallels with SUDs. Eight main themes emerged from a thematic qualitative analysis; compulsivity as central to AN, impaired control, escalating compulsions, emotional triggers, reactions to prevention, detrimental continuation, functional impairment, and role in recovery. These themes suggested that some individuals with AN view the compulsive nature of their behaviour as central to the maintenance of their disorder, and as a significant barrier to recovery. A number of these individuals also acknowledge the detrimental effect this behaviour has on their psychological health, and on their ability to function effectively in everyday life, however they feel unable to control their behaviour despite this. In line with suggestions of a parallel with compulsive drug-seeking behaviour (Barbarich-Marsteller et al., 2011; Kaye, Wierenga, Bailer, Simmons, Wagner, et al., 2013; Park, Godier, & Cowdrey, 2014; Scheurink et al., 2010; Zink & Weinberger, 2010), the qualitative themes showed a number of similarities with the characteristic behaviours of substance dependence, and appear to map on to DSM-V criteria for SUDs. Indeed, some participants made a direct comparison to addiction, describing themselves as analogous to an individual addicted to a substance. The parallels observed between the qualitative themes and the criteria for SUDs are shown in Table 2.3, and will now be discussed in reference to each of the four groups of criteria; impaired control, social impairment, risky use of substance, and pharmacological criteria.

2.8.1 Impaired control

The impaired control criteria for SUDs refer to an individual experiencing cravings or a strong desire to use the substance, persistent desire/unsuccessful attempts to cut down

or control substance use, alongside increasing amounts or periods of time spent taking the substance, and a great deal of time spent carrying out activities relating to substance use. Theme two of this study (impaired control), which was endorsed by 62.5% (25/40) of participants, suggested that the majority of participants in this study felt impaired control over their behaviour. Participants reported feeling trapped or controlled by their disorder, and described the desire/attempts to disengage from compulsive weight-loss behaviours. Furthermore, 35% (14/40) of participants also reported an escalation of compulsive behaviour over time (theme three, escalating compulsions), with weight-loss goals and behaviours increasing over time in a similar way to the increasing amount/time over which a substance is taken.

The lack of control described by the majority of participants over these behaviours is striking, and relevant to recent theoretical accounts of the persistence of behaviour in AN (Steinglass & Walsh, 2006; Walsh, 2013). As discussed in Section 1.9, Walsh (2013) proposes that excessive habit formation may contribute to the development and maintenance of compulsive behaviours in AN. Habitual behaviour is highly resistant to change, which may reflect participants feeling unable to control or disengage in these behaviours in this study. A shift in balance away from goal-directed control and towards excessive habit learning has been shown in substance dependence, and may be relevant to the compulsive and persistent nature of behaviour in AN (Steinglass & Walsh, 2006; Walsh, 2013).

2.8.2 Social impairment

The social impairment criteria for SUDs refer to continued substance use, resulting in a failure to fulfil major obligations relating to work/school and home, a reduction in or giving up of important social, occupational, or occupational activities, and social or

interpersonal problems caused or exacerbated by substance use. In theme three of this study (functional impairment) 37.5% (15/40) of participants described the time consuming nature of their weight-loss compulsions, and the detrimental effect this had on their family, social and occupational lives. Weight-loss behaviours appear to become the most important priority in these individuals' lives, in a similar way to drug-seeking behaviours in SUDs, to the detriment of the psychological and physical health, as well as their interpersonal and occupational functioning.

2.8.3 Risky use of substance

Risky use of substance in SUDs refers to recurrent use in situations in which it is physically hazardous, and continued use despite knowledge of a physical or psychological problem relating to substance use. In theme 4 of this study (detrimental continuation), which was endorsed by 45% (18/40) of participants, psychological distress as a direct result of continued compulsive weight-loss behaviour was acknowledged. However, participants described feeling unable to cease these behaviours despite this. Indeed reluctance to recover is often reported in AN, and has been linked to the ego-syntonic nature of symptoms in AN, and feeling as though the benefits of having AN outweigh the negatives (Nordbø et al., 2012).

Whilst speculative, it may be that in both AN and SUDs the pursuit of a rewarding outcome associated with the behaviour (i.e. weight-loss or drug-induced 'high') may be seen to outweigh the adverse consequences of behaviour and lead to continuation of this behaviour. Indeed, some participants described the pursuit of positive emotions, such as safety and control, as important maintaining factors of compulsive weight-loss behaviours. As discussed in Section 1.9, in the early rewarding effects both of food restriction and drug-taking may cause these behaviours to be repeated and become habitual/compulsive in

nature (Walsh, 2013; Zink & Weinberger, 2010). It is possible that disorder-related cues in AN gain incentive salience and trigger disorder-related compulsions in a similar way to drug-related cues in SUDs (Zink & Weinberger, 2010). For example, one participant described the way in which their behaviour could be triggered by walking past someone thin, or seeing images of thin celebrities in magazine, further supporting this idea. This rewarding aspect of disorder-related behaviour in AN is also consistent with the formation of habits in AN, in which initially rewarding weight-loss behaviour becomes habitual once over trained, and can be triggered by related environmental cues (Walsh, 2013).

2.8.4 Pharmacological criteria

The 'pharmacological' criteria for SUDs refer to tolerance to and withdrawal from the substance. Tolerance in SUDs is defined as the need to use increasing amounts of the substance to achieve the same level of intoxication, or a diminished effect with continued use of the same amount of the substance (American Psychiatric Association, 2013). In so called 'behavioural addictions' it can be argued that behavioural features of tolerance may be manifest, in the absence of clear pharmacological mechanisms (Blaszczynski, Walker, Sharpe, & Nower, 2008). Indeed, at a behavioural level, the concept of tolerance may parallel the escalating nature of compulsions described by AN participants in theme five (escalating compulsions), in which a number of individuals with AN (35%, 14/40) reported feeling the need to increase weight-loss goals/behaviours over time.

The majority of participants (72.5%, 29/40) reported a strong negative reaction to being prevented from performing compulsive behaviours, most commonly in the form of negative emotions such as anxiety and guilt, but also physical feelings such as agitation, restlessness and in one case tachycardia (theme six; negative reactions). This may be comparable to the withdrawal symptoms experienced by individuals with SUDs, although

withdrawal from a physical substance is acknowledged to be much more extreme. Forty percent of participants also suggested that both the avoidance of negative emotions, such as anxiety and fear of fatness, and the pursuit of positive emotions, such as safety and control, were important in triggering compulsive weight-loss behaviours (theme seven; emotional triggers). This raises the possibility that compulsive weight-loss behaviour in AN may be used as a maladaptive emotion-regulation strategy, used to attenuate or avoid negative emotions (Harrison, Sullivan, Tchanturia, & Treasure, 2010; Merwin et al., 2011; Wildes et al., 2010). Indeed drug use has been described as means of regulating emotions (Kober & Bolling, 2014), and this may serve to further reinforce compulsive behaviour in both SUDs and AN.

However, these findings also support a role for positive reinforcement in AN, which has previously been conceptualised as a disorder centred around anhedonia and the avoidance of negative affect associated with food (Kaye et al., 2003; Zink & Weinberger, 2010). Indeed, recent fMRI studies have provided evidence of increased positive feelings and corresponding activation in reward areas of the brain in response to disorder-related stimuli in AN (Fladung et al., 2010; Fladung et al., 2013). A model in which the pursuit of positive emotions, such as feelings of pride and accomplishment, reinforce and drive further weight-loss behaviour in AN has been suggested by Selby et al (2013). This model posits that individuals with AN have low positive emotion differentiation, defined as the ability to differentiate between discrete positive emotions, and as a result a wide range of positive emotions are activated with weight loss. Over time, weight-loss behaviour is conditioned to elicit positive emotions regardless of whether further weight loss is attained (Selby et al., 2013). The underlying premise of this theory is consistent with that of Walsh's (2013) habit formation theory, in which initially rewarding weight-loss behaviour becomes habitual once over-trained, and weight loss in no longer required for this

behaviour to be elicited (Walsh, 2013). It may be that in both AN and substance dependence the early rewarding effects of food restriction and drug-taking may both cause these behaviours to be repeated and become habitual/compulsive in nature (Zink & Weinberger, 2010).

2.8.5 Limitations

Considering the lack of research looking at the possible parallels between the compulsive nature of behaviour in AN and SUDs, qualitative data capturing the subjective experience of compulsive weight-loss behaviours may be an important stepping-stone in identifying avenues for future research and treatment development. However, some important limitations of this research should be acknowledged. Compulsive behaviour was not defined prior to the prompt questions, as this concept was introduced prior to the study, and as such it is possible that there may have been discrepancies in participants understanding of this concept. Additionally, whilst the prompt questions used were designed to direct responses towards the compulsive nature of behaviour in AN for the purpose of the study, the wording of these prompt questions is likely to have biased participants' responses. These questions assumed participants agreement that their behaviour is compulsive, reducing the likelihood of participants discussing other potentially important symptoms. Furthermore, the deductive nature of the qualitative analysis, which was carried out with certain hypotheses in mind, is likely to have led to a selection bias in the excerpts used and the themes extracted from the data. It is also true that some themes were more highly endorsed by participants than others (See Table 2.2). This should be considered when making a comparison to SUDs, as some parallels may be more widely relevant to AN than others. For example, whilst theme six (reactions to prevention) was endorsed by 72.5% (29/40) of participants, theme three (functional impairment) was endorsed by only 37.5% (15/40) of participants.

A more general limitation of this study was the reliance on self-report, both in terms of participants responses, and the identification of a sample of individuals with a current diagnosis of AN. This reliance on self-report may have led to inaccurate responses. This may be particularly relevant for individuals with AN, given evidence that those with AN may have low interoceptive awareness, characterised by uncertainty in the recognition of emotional states, and an inability to discriminate between sensations such as hunger and satiety (Fassino, Pierò, Gramaglia, & Abbate-Daga, 2004). As such they may be unable to describe or report their subjective experiences accurately.

The use of qualitative analysis should be interpreted with caution, as this methodology relies on participants choosing to disclose certain information and personal stories, and is not directly supported by statistical analysis. However, qualitative analysis may help inform and inspire future research questions, particularly when combined or supported by quantitative methodologies.

The use of an online system may also be considered a limitation as this does not allow for follow up questions or clarification of responses as in interview settings. As participants were also recruited for the study reported in Chapter 3, sampling was not guided by the achievement of data saturation. However, the number of participants recruited is large compared to most qualitative studies, and it is felt that data saturation was achieved in the current sample, as new themes were no longer seen to be emerging by the end of transcript coding. It is however acknowledged that further participant recruitment may have resulted in the emergence of novel themes.

2.8.6 Conclusions

When asked to reflect on the compulsive nature of their behaviour, the majority of participants with AN described having little control over their behaviour, and some

reported an escalation of weight-loss behaviour and goals over time. Some also acknowledged the detrimental effect this behaviour has on their psychological health, and on their ability to function effectively in everyday life, yet they continued to feel unable to cease this behaviour. Participants' experience of compulsivity in AN appears to map on to the DSM-V criteria for SUDs, supporting increasing suggestion of parallel between these disorders, and conceptualization of compulsivity as a transdiagnostic concept. Further research is needed to explore the behavioural and neural underpinnings of compulsivity in AN, and it's relation to other compulsive disorders such as substance dependence. In particular, these results support further investigation of parallels with the role of maladaptive habit learning in AN, which is shown to be dysfunctional in substance dependence and other compulsive disorders. Conceptualising compulsive behaviour in AN as a transdiagnostic concept in this way may open up novel treatment avenues for AN, in which existing treatments targeting habitual and compulsive behaviours could be utilised for the treatment of AN.

3. Development and validation of two novels measures of compulsive behaviour in Anorexia Nervosa: The Self-Starvation Scale and the Compulsive Exercise Scale.

3.1 Overview

Chapter 2 showed how the subjective experience of compulsive weight-loss behaviour in AN can be considered to be comparable to the characteristic behaviours inherent in substance dependence, and in particular map onto the DSM-V criteria for SUDs. This supports recent theories suggesting parallels between AN and other compulsive disorders, and provides preliminary evidence for trandiagnostic significance of compulsivity across disorders. To further investigate the behavioural parallels between AN and other compulsive disorders, this chapter will explore the utility of adapting the criteria for SUDs to capture compulsive weight-loss behaviours in AN. Two novel measures of self-starvation and excessive exercise behaviour are developed and validated in both a community sample (Study 1), and a sample of individuals with experience of AN (Study 2). The following questions will be addressed:

- Can the criteria for substance dependence be adapted and used to capture compulsive weight-loss behaviours?
- Is this approach effective in capturing compulsive weight-loss behaviour in both a community sample of healthy volunteers, and in a sample of individuals with experience of AN (current and past)?

3.2 Background

In Chapter 2 it was shown that the subjective experience of compulsivity in AN could be seen to map onto the DSM-V criteria for SUDs, reflecting an increase in suggestion of parallels between the disorders in recent literature (Barbarich-Marsteller et al., 2011; Kaye, Wierenga, Bailer, Simmons, Wagner, et al., 2013; Park et al., 2014; Zink & Weinberger, 2010). Substance dependence has been described as a persistent state in which there is a lack of control over compulsive drug-seeking, and a lack of regard for the risk of serious negative consequences (Hyman & Malenka, 2001). As discussed in Section 1.7.1, this appears to parallel the relentlessness with which individuals with AN pursue weight loss, despite the profoundly negative physiological and psychological consequences it has for them.

The compulsive nature of behaviour across these disorders may be the result of the aberrant reward processing for disorder-related stimuli, which has been documented in both AN (Cowdrey, Finlayson, & Park, 2013; Cowdrey et al., 2011; Fladung et al., 2010), and substance dependence (Goldstein & Volkow, 2002). Disorder-related reward may become highly motivationally salient and promote the development of compulsive disorder-related behaviour. An overreliance on habit formation in behavioural learning has been suggested to underlie the development of compulsive behaviour in AN (Steinglass & Walsh, 2006; Walsh, 2013) and substance dependence (Everitt & Robbins, 2005; Ostlund & Balleine, 2008).

Shared neurobiological abnormalities in reward circuits across AN and substance dependence also support this notion. Neuroimaging studies show increases in activity in brain regions associated with the motivational value of reward in response to disorder-related stimuli in both disorders (Cowdrey et al., 2011; Fladung et al., 2010; Fladung et al.,

2013; Goldstein & Volkow, 2002), suggesting they may share dysfunction in brain reward circuits, which favour disorder-relevant reward at the expense of other natural reinforcers. This is supported by a dysregulation of DA in both disorders (See Section 1.8.2). These aberrancies in reward processing may play a part in triggering compulsive behaviour, which could help explain the high level of chronic relapse observed in substance dependence (Cami & Farre, 2003), and the persistence of restrictive behaviour in AN, which is highly resistant to change (Mayer, Schebendach, Bodell, Shingleton, & Walsh, 2012). Dysregulated reward processing and habit formation (see Section 1.9) are possible candidates for common pathological processes underpinning compulsivity across these disorders. A transdiagnostic theory of compulsivity across disorders could help to explain these similarities at the level of pathological processes (Robbins et al., 2012), thus opening up novel avenues for treatment development focused on such processes.

There is a paucity of standardised self-report measures of compulsive behaviour in EDs such as AN. Considering the similarities reported in Chapter 2 between the compulsive behaviours seen in AN and those of substance dependence, and the dysfunction in reward and neural abnormalities seen in both disorders, it may be useful to use the concept of dependence when measuring compulsive weight-loss behaviours. For that reason, two new measures of self-starvation and compulsive exercise were created by adapting the questions of the Yale Food Addiction Scale (YFAS) (Gearhardt et al., 2009) for these constructs. The YFAS is a previously validated questionnaire that uses an adaptation of the criteria of substance dependence from the DSM-IV-TR to measure addiction to food. The concept of 'food addiction', in which individuals engage in compulsive overeating, has also been compared to the maladaptive cycle of substance dependence (Corwin & Grigson, 2009; Davis & Carter, 2009), and may be relevant in eating disorders dominated by binge-eating such as BN, binge/purge AN, and BED

(Cassin & von Ranson, 2007). The existence of 'food addiction' is the subject of continued debate, and would appear to be opposite in nature to the compulsive under-eating, self-starvation behaviour seen in AN. This chapter aims to use the criteria for substance dependence on which the YFAS was modelled, to develop and validate measures of compulsive weight-loss behaviour. Using this dependence-related criteria for self-starvation and compulsive exercise may allow the useful measurement of the persistence and compulsivity of core features of EDs such as AN.

Relentless food restriction is a universal and characteristic feature of AN, whereas compulsive exercise may also be highly relevant to individuals without an ED diagnosis, such as those involved in competitive sports. These individuals may be considered more likely to show higher levels of sub-clinical ED symptoms, with evidence of elevated ED symptoms in elite athletes in comparison to the general population (Martinsen & Sundgot-Borgen, 2013; Sundgot-Borgen & Torstveit, 2004). For that reason, a group of individuals involved in competitive sports were included in the community sample in order to try and capture this behaviour fully in healthy individuals. Including this group in the community sample may help to validate these measures by including individuals with subclinical ED symptoms.

3.3. Study 1: Validation of the Self-Starvation and Compulsive Exercise Scales in a community sample.

3.3.1 Study 1: Aims

- To design and validate measures of compulsive self-starvation and compulsive exercise in a community sample.
- To investigate the internal consistency and test-retest reliability of the Self-Starvation (SS) and Compulsive Exercise Scales (CES).
- To explore the convergent and predictive validity of the SS and CES, with previously validated measures of depression and anxiety, ED symptoms, experiential avoidance, food addiction, excessive exercise, impulsivity and substance addiction.

3.3.2. Study 1: Hypotheses

- The new measures will be independently predictive of ED symptoms, when controlling for other validated self-report measures.
- Individuals involved in competitive sports will score more highly on the new measures than those not involved in competitive sports.

3.3.3 Study 1: Methods

3.3.3.1 Participants

One hundred and twenty-six participants between the ages of 18-65 were recruited for a community sample of healthy individuals. This group was the split during analysis according to those who currently take part in competitive sports (CS group, n=54) and those who do not (HC group, n=72). Participants were recruited via email, internet and poster advertisement. Participants were excluded if they had previously been diagnosed with an eating disorder. There were no other inclusion/exclusion criteria.

3.3.3.2 Study Procedure

The research protocol was reviewed and approved by the University of Oxford's Research Ethics Committee (MSD-IDREC-C1-2013-039 (224); see Appendix 3.1). The set of online questionnaires was created using Bristol Online Surveys (BOS; Institute of Learning and Research Technology, University of Bristol, UK). The questionnaires included the new SS and CES as well as a number of other self-report measures of depression, anxiety, eating disorder symptoms, experiential avoidance, food addiction, excessive exercise, impulsivity and substance abuse (described below). Participants were initially emailed an information sheet (see Appendix 3.2) and asked a number of questions via email to ensure eligibility to the study. They were then sent a consent form (see Appendix 3.3) to complete before being provided with a link to the online set of questionnaires. The questionnaires took approximately 25 minutes to complete. Half of the participants were subsequently contacted and asked to complete the new SS and CES again to assess test-retest reliability. The second set of questionnaires took approximately 10 minutes to complete. Data was stored automatically from the online programme, and all data was analysed using SPSS.

Participants were compensated with a £5 Amazon voucher for each set of questionnaires completed.

3.3.3.3 Measures

Self-Starvation Scale (SS) and Compulsive Exercise Scale (CES): Two new measures of self-starvation (SS; see Appendix 3.6) and compulsive exercise (CES; see Appendix 3.7) were developed by adapting the questions of the previously validated Yale Food Addiction Scale (YFAS) (Gearhardt et al., 2009) for these compulsive behaviours in EDs. The YFAS was used to aid development as this measure uses an adaptation of the criteria of substance dependence from the DSM-IV-TR to measure addiction to food. Using a measure that draws on addictive behaviours may help to usefully measure these aspects of AN by capturing the compulsive nature of the behaviours.

The rating scales were adapted from the original YFAS scales to mirror that of the EDE-Q, as it was felt this scale was more relevant to ED pathology. The resulting questionnaires consist of 17-items which ask participants to choose the corresponding number of days out of 28 days (4 weeks) on a 7 point scale, in which each of the statements has applied to them. A further 8 questions asked participants to answer yes or no to indicate whether or not the statement applied to them.

Participants were also asked to provide feedback on the structure and content of the new questionnaires to aid in further development. Participant feedback suggested that the dichotomous items were difficult to answer, and did not usefully capture the measured behaviours. For this reason it was decided that only the likert items would be analysed.

Patient Health Questionnaire-9 (PHQ-9): The PHQ-9 (Kroenke, Spitzer, & Williams, 2001) is a 9-item scale designed to assess severity of depression over the past 2 weeks (see Appendix 3.8). Scores of 5, 10, 15 and 20 represent cut off points for mild, moderate,

moderately severe, and severe depression respectively. It has been shown to have good validity and reliability (Kroenke et al., 2001).

Generalised Anxiety Disorder Assessment–7 (GAD-7): The GAD-7 (Spitzer, Kroenke, Williams, & Lowe, 2006) is a 7-item scale designed to assess the presence of generalised anxiety disorder symptoms over the past two weeks (see Appendix 3.9). Scores of 5, 10 and 15 represent cut off points for mild, moderate and severe anxiety respectively. It has been shown to have good reliability, as well as good criterion, construct, factorial and procedural validity (Spitzer et al., 2006).

Eating Disorder Examination - Questionnaire (EDE-Q): (Fairburn & Beglin, 2008) See Section 2.3.3 and Appendix 2.4.

Clinical Impairment Assessment (CIA): (Bohn & Fairburn, 2008) See Section 2.3.3 and Appendix 2.5.

The Acceptance and Action Questionnaire-II (AAQ-II): The AAQ-II (Bond et al., 2011) is a 7-item self-report measure of experiential avoidance and psychological inflexibility (see Appendix 3.10). It asks participants to rate on a 7-point scale how true each of the statements is for them, with higher scores reflecting greater levels of avoidance and psychological inflexibility. The AAQ-II was designed as a brief measure of the same constructs as the original AAQ-I (Hayes et al., 2004), and correlates well with the original measure (Bond et al., 2011).

Yale Food Addiction Scale (YFAS): The YFAS (Gearhardt et al., 2009) is a 27-item self-report measure designed to identify those exhibiting signs of addiction towards certain types of food, such as those with high fat and high sugar content (see Appendix 3.11). The content of the questions is based upon the substance dependence criteria of the DSM-IV-

TR (American Psychiatric Association, 2000). Scoring reflects the presence or absence of each of these criteria in reference to food addiction. It has been shown to have adequate internal reliability, and good convergent and discriminant validity (Gearhardt et al., 2009).

Compulsive Exercise Test (CET): The CET (Taranis, Touyz, & Meyer, 2011) is a 24-item self-report measure designed to assess the core features of excessive exercise in EDs (see Appendix 3.12) . As well as a global score, the CET is comprised of five subscales: avoidance and rule driven behaviour, weight control exercise, mood improvement, lack of exercise enjoyment, and exercise rigidity. Participants are asked to rate on a 6 point likert scale, with higher scores indicating greater pathology. It has been shown to have high internal consistency, and correlates with other measures of excessive exercise and eating disorder pathology (Taranis et al., 2011).

Barratt Impulsiveness Scale (BIS-11): The BIS-11 (Patton, Stanford, & Barratt, 1995) is a 30-item self-report measure designed to assess the personality/behavioural construct of impulsiveness (see Appendix 3.13). Participants are asked to use a 4-point scale to rate how often each statement applies to them. As well as a global score, the BIS-II is made up of 3 subscales: attentional impulsiveness, motor impulsiveness, and non-planning impulsiveness. It has been shown to be internally consistent (Patton et al., 1995), and has good test-retest reliability, and convergent and concurrent validity (Stanford et al., 2009).

Leeds Dependence Questionnaire (LDQ): The LDQ (Raistrick et al., 1994) is a 10-item self-report measure, developed from the ICD-10 definitions of substance dependence (see Appendix 3.14). Participants are asked to think about their drug of concern and rate answers on a 4-point scale. A higher score reflects a higher level of dependence. It has been found to have good internal consistency and excellent test-retest reliability (Raistrick et al., 1994).

Other information: Participants also provided demographic information (gender, age, language, occupation) and self-reported height and weight (in order to calculate BMI = weight[kg]/height [m^2]).

3.3.4. Study 1: Demographic Results

Data was collected from 126 participants, 54 were currently involved in competitive sport (CS group) and 72 were not (HC group). 80% (101/126) of these participants in the community sample spoke English as a first language, and all were fluent in English comprehension. Gender distribution in this sample was 65% female (82/126) and 35% male (44/126). A wide range of occupations were reported, with the majority (59.5%) reporting to be students (75/126). Demographic and psychological characteristics of the community sample can be found in Table 3.1. One-Way ANOVAs were used to look at significant differences between the CS and HC groups. These groups differed only on measures of compulsive exercise (CES and CET) and on the AAQ, a measure of experiential avoidance.

Table 3.1: Demographic and Psychological Characteristics

	All Participants (N=126)		***CS Group (N=54)***		***HC Group (N=72)***		***One-Way ANOVA***
Measure	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P-Value**
Age	26.32	8.17	25.35	8.95	27.04	7.51	.252
BMI	22.81	3.14	22.87	2.69	22.76	3.46	.852
EDE-Q	1.46	1.28	1.49	1.42	1.43	1.17	.810
CIA	6.84	8.20	7.26	8.51	6.53	8.01	.622
YFAS Symptom Count	1.57	1.20	1.39	0.76	1.71	1.44	.141
YFAS Diagnostic	0.06	0.25	0.06	0.23	0.07	0.26	.754
CET	11.11	3.57	12.04	3.48	10.41	3.50	**.011**
BIS	60.21	11.05	58.80	9.73	61.28	11.90	.214
AAQ-II	46.80	9.48	48.96	9.31	45.18	9.35	**.026**
GAD-7	5.15	4.91	4.87	4.46	5.36	5.24	.580
PHQ-9	4.74	4.77	4.02	4.01	5.28	5.23	.143
LDQ	1.75	3.11	1.72	2.74	1.76	3.37	.941
SS	7.38	11.96	9.04	13.15	6.14	10.92	.179
CES	11.33	13.95	18.44	16.72	5.99	8.15	**<.001**

Note: BMI = Body Mass Index; EDE-Q = Eating Disorder Examination-Questionnaire; CIA = Clinical Impairment Assessment; OxBread = Oxford Brain – Body Research into Eating Disorders Scale; YFAS = Yale Food Addiction Scale; CET = Compulsive Exercise Test; BIS = Barratt Impulsiveness Scale; AAQ-II = Action and Acceptance Questionnaire II; GAD-7 = Generalised Anxiety Disorder Assessment-7; PHQ-9 = Patient Health Questionnaire-9; LDQ = Leeds Dependence Questionnaire; SS = Self-Starvation Scale; CES = Compulsive Exercise Scale.

3.3.5 Study 1 Results: The Self-Starvation Scale (SS)

3.3.5.1 Principal Components Analysis

PCA yielded 4 factors based on eigenvalues (8.33, 1.54, 1.20, 1.09). Plotting of the factors and examining the factor loadings suggested that a one factor structure may be optimal. The scree plot can be seen in Figure 3.1, and the factor loadings in Table 3.2. This factor accounted for 48.97% of the variance. One item was excluded at this point as it had a low factor loading (Q25). This factor structure had good internal consistency (α =.92, average inter-item correlation = .48), and test-restest reliability (*r*= .98, p<.01).

Figure 3.1. Scree Plot showing the eigenvalues and components for the Self – Starvation Scale

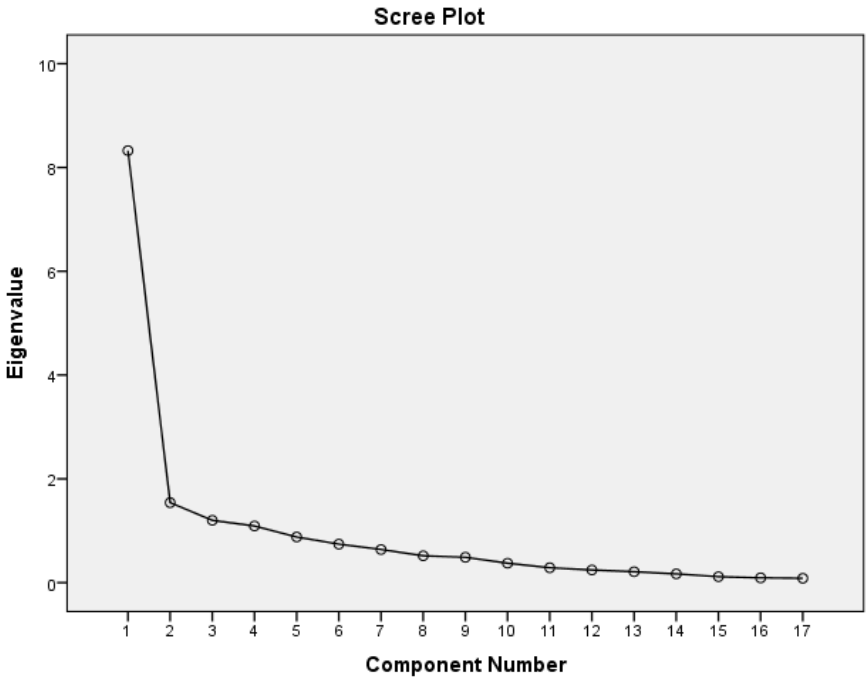


Table 3.2. Item factor loadings for the Self-Starvation Scale

Item	In the past four weeks….	Factor Loading
Q8	I have restricted my food intake so much that I have concentrated on this instead of doing other activities.	.830
Q12	I have had withdrawal symptoms such as agitation, anxiety, or other physical symptoms when I have been unable to restrict my food intake.	.792
Q13	I have restricted my food intake to prevent feelings of anxiety, agitation, or other physical symptoms that were developing.	.786
Q7	I find that when I am unable to restrict my food intake, I will go out of my way to find a way to do so.	.786
Q2	I find myself continuing to restrict my food intake, even though I am hungry.	.757
Q15	My behaviour with respect to restricting my food intake causes significant distress.	.754
Q6	I find myself constantly restricting my food intake throughout the day.	.753
Q9	I have spent time dealing with negative feelings from restricting instead of doing other activities e.g. working, spending time with family or friends.	.749
Q14	I have found that I have an elevated desire or urges to restrict my food intake.	.720
Q4	Not restricting my food intake or having to eat more food is something I worry about.	.693
Q3	I restrict my food intake to the point where I feel physically ill.	.659

Q5	I spend a lot of time feeling sluggish or fatigued from restricting my food intake.	.641
Q1	I find that when I start restricting my food intake, I end up restricting much more than I planned.	.639
Q11	I have avoided professional or social situations involving food because I felt I would be unable to restrict certain foods.	.639
Q10	I have avoided professional or social situations involving food because I was afraid I would restrict my food intake.	.636
Q16	I experience significant problems in my ability to function (job/school, social or family activities) because of restricting my food intake.	.558
Q25	How many days in the past four weeks have you tried to stop restricting your food intake?	.367

3.3.5.2 Construct Validity

As all but one of the study variables were not normally distributed (Kolmogorv-Smirnov = $p<.05$), non-parametric Spearman's Rho (*r*) was used to examine the association between the study variables using data from all participants. Significance levels were corrected for multiple comparisons.

Convergent validity was assessed by correlating scores from the SS with measures of ED symptoms and excessive exercise. Significant positive correlations were found between SS scores and the EDE-Q subscale scores, the CIA, and the CET. Table 3.3 shows the convergent correlation coefficients for the sample.

Table 3.3 Convergent correlations between the Self-Starvation Scales and measures of ED symptoms

Spearmans rho *r*	**SS**	**EDE Global**	**EDE Restraint**	**EDE Eating**	**EDE Shape**	**EDE Weight**	**CIA**	**CET**
SS	1.00	**.707***	**.672***	**.619***	**.630***	**.644***	**.562***	**.506***
EDE Global		1.00	**.848***	**.868***	**.951***	**.944***	**.715***	**.530***
EDE Restraint			1.00	**.678***	**.721***	**.705**	**.573***	**.488***
EDE Eating				1.00	**.798***	**.803***	**.692***	**.416***
EDE Shape					1.00	**.908***	**.660***	**.526***
EDE Weight						1.00	**.676***	**.487***
CIA							1.00	**.496***
CET								1.00

Note: * = $p<.001$; EDE-Q = Eating Disorder Examination-Questionnaire; CIA = Clinical Impairment Assessment; CET = Compulsive Exercise Test; SS = Self-Starvation Scale.

Discriminant validity was assessed by correlating the scores from the SS with other independent constructs (impulsivity, substance dependence and BMI). The SS did not correlate with any of these constructs. Table 3.4 shows the divergent correlation coefficients for the sample.

Table 3.4 Divergent correlations between the Self-Starvation Scale and measures of impulsivity, substance dependence and BMI.

Spearmans rho *r*	**SS**	**BIS**	**LDQ**	**BMI**
SS	1.00	.011	.096	.104
BIS		1.00	.135	.074
LDQ			1.00	.206
BMI				1.00

Note: SS = Self-Starvation Scale; BMI = Body Mass Index; BIS = Barratt Impulsiveness Scale; LDQ = Leeds Dependence Questionnaire;

Scores on the YFAS did correlate significantly with scores on the SS, although the size of the correlation was small (r =.40). Once the individuals who reported binge eating episodes (n=54) were removed, no significant correlation was seen (r =.189).

3.3.5.3 Ability to predict ED symptoms

Stepwise regression was used to assess the ability of the SS to predict EDE-Q scores when controlling for the common variance associated with clinical impairment, depression, anxiety and BMI. On Step 1, only the CIA scores were entered into the model, R^2= .58, F=173.40, p <.001. In the final model, it was shown that the SS made additional

significant contributions to the model, R^2 = .62, F= 12.96, p= <.001). Table 3.5 shows the final model for the prediction of the EDE-Q scores by the SS.

Table 3.5 Final model for the prediction of the EDE-Q scores by the Self-Starvation Scale.

Variable	ß (standardised)	*T*	*p*
Constant		6.68	<.001
CIA	.598	8.31	<.001
SS	.259	3.60	<.001
PHQ-9	-.017	-.232	.817
GAD-7	-.032	-.468	.641
BMI	.097	1.722	.088

Note: BMI = Body Mass Index; CIA = Clinical Impairment Assessment; GAD-7 = Generalised Anxiety Disorder Assessment-7; PHQ-9 = Patient Health Questionnaire-9; SS = Self-Starvation Scale.

3.3.5.4. Application in the competitive sports group

Individuals in the competitive sports group reported higher scores on the SS (mean=9.04, SD= 13.15), compared to those not involved in competitive sport (mean = 6.14, SD = 10.92) but this did not reach significance (Kruskal-Wallis [χ2=.563 p=.453]).

3.3.6 Study 1 Results: The Compulsive Exercise Scale (CES)

3.3.6.1. Principal Components Analysis

PCA yielded 4 factors based on eigenvalues (7.70, 1.44, 1.40, 1.10). Plotting of the factors and examining the factor loadings suggested that a one factor structure may be optimal. The scree plot can be seen in Figure 2, and the factor loadings in Table 3.6. Two factors were excluded at this point as they had low factor loadings (Q10 and Q25). This one factor structure accounted for 45.32% of the variance, had good internal consistency (α =.92, average inter-item correlation = .76), and test-restest reliability (r= .70, p<.01).

Figure 3.2. Scree Plot showing the eigenvalues and components for the Compulsive Exercise Scale

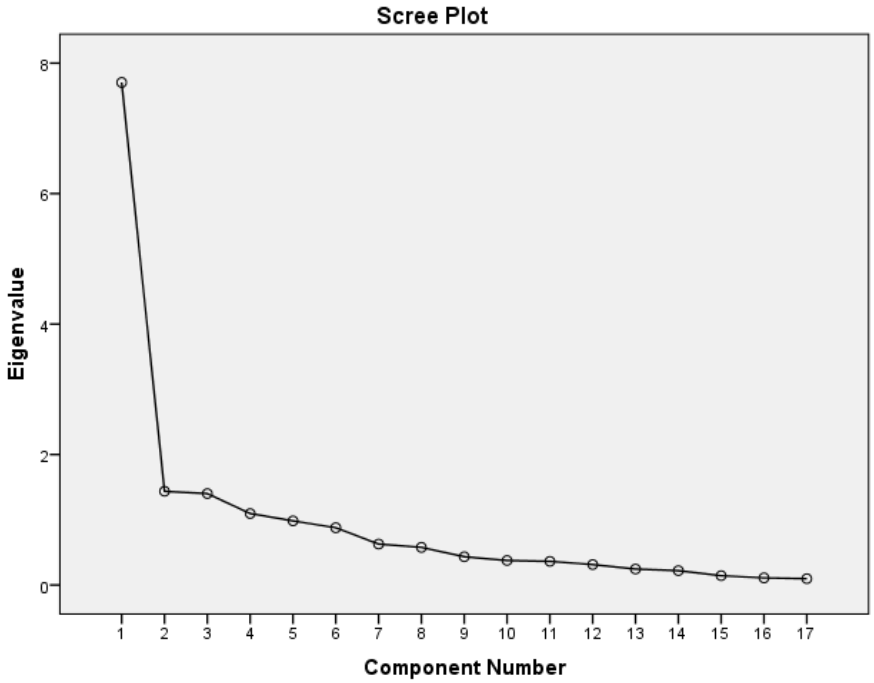


Table 3.6 Item factor loadings for the Compulsive Exercise Scale

Item	In the past four weeks….	Factor Loading
Q12	I have had withdrawal symptoms such as agitation, anxiety, or other physical symptoms when I have been unable to exercise.	.876
Q11	I have avoided professional or social situations because I would not be able to exercise.	.840
Q7	I find that when I am unable to exercise, I will go out of my way to find a way to do so.	.812
Q14	I have found that I have an elevated desire or urges to exercise.	.804
Q8	I have focused on exercise so much that I have concentrated on this instead of doing other activities.	.801
Q9	I have spent time dealing with negative feelings from exercising instead of doing other activities e.g. working, spending time with family or friends.	.794
Q16	I have experienced significant problems in my ability to function job/school, social or family activities) because of exercise.	.744
Q13	I have exercised to prevent feelings of anxiety, agitation, or other physical symptoms that were developing.	.736
Q4	Not being able to exercise is something I worry about.	.704
Q6	I find myself constantly trying to exercise throughout the day.	.690
Q15	My behaviour with respect to exercising causes significant distress.	.651
Q2	I find myself continuing to exercise, even when I am too tired to do so.	.578
Q1	I find that when I start to exercise, I end up exercising more than I planned.	.559
Q3	I exercise to the point where I feel physically ill.	.494
Q5	I spend a lot of time feeling sluggish or fatigued from exercise.	.492
Q10	I have avoided professional or social situations where exercise was available; because I was afraid I would over exercise.	.184
Q25	How many times in the past four weeks have you tried to stop exercising?	.162

3.3.6.2 Construct Validity

Convergent validity was assessed by correlating scores from all participants on the CES with measures of compulsive exercise and ED symptoms, using non-parametric Spearman's correlation coefficients. Bonferroni corrected significant positive correlations were found between the CES and the CET scores, particularly the CET Rule Driven subscale. There were no significant correlations between CES and EDE-Q scores. There was a significant correlation with CIA scores, although the absolute value of was low. Table 3.7 shows the convergent correlation coefficients.

Table 3.7 Convergent correlations between the Compulsive Exercise Scale and measures of compulsive exercise and ED symptoms

Spearman's rho *r*	CES	CET	CET Rule Driven	CET Weight Control	CET Mood Improvement	CET Lack of Enjoyment	CET Rigidity	EDE-Q	CIA
CES	1.00	**.536***	**.754***	.155	**.548***	**-.359***	**.487***	.258	**.341***
CET		1.00	**.759***	**.695***	**.616***	-.016	**.703***	**.530***	**.496***
CET Rule Driven			1.00	**.344***	**.606***	-.280	**.577***	.305	**.362***
CET Weight Control				1.00	.264	0.31	.266	**.753***	**.468***
CET Mood Improvement					1.00	**-.379***	**.448***	.130	.179
CET Lack of Enjoyment						1.00	-.234	.115	.133
CET Rigidity							1.00	.119	**.499***
EDE-Q								1.00	.201
CIA									1.00

Note: * = p<.001 BMI = Body Mass Index; EDE-Q = Eating Disorder Examination-Questionnaire; CIA = Clinical Impairment Assessment; OxBread = Oxford Brain – Body Research into Eating Disorders Scale; YFAS = Yale Food Addiction Scale; CET = Compulsive Exercise Test; BIS = Barratt Impulsiveness Scale; AAQ-II = Action and Acceptance Questionnaire II; GAD-7 = Generalised Anxiety Disorder Assessment-7; PHQ-9 = Patient Health Questionnaire-9; LDQ = Leeds Dependence Questionnaire; CES = Compulsive Exercise Scale.

Discriminant validity was assessed by correlating CES scores with other independent constructs (impulsivity, substance dependence and BMI). The CES did not correlate with any of these constructs. Table 3.8 shows the divergent correlation coefficients.

Table 3.8 Divergent correlations between the Compulsive Exercise Scale and measures of impulsivity, substance dependence and BMI.

Spearmans rho *r*	**CES**	**BIS**	**LDQ**	**BMI**
CES	1.00	.052	.113	.145
BIS		1.00	.135	.074
LDQ			1.00	.206
BMI				1.00

Note: BMI = Body Mass Index; BIS = Barratt Impulsiveness Scale; LDQ = Leeds Dependence Questionnaire; CES = Compulsive Exercise Scale.

Scores on the YFAS did correlate significantly with scores on the CES, although the size of the correlation was small (r =.27). Once the individuals who reported binge eating episodes (n=54) were removed, no significant correlation was seen (r =.20).

3.3.6.3 Ability to predict clinical impairment

As the CES did not correlate with the EDE-Q, but did correlate significantly with scores of clinical impairment, a stepwise regression analysis was used to test the ability of the CES to predict CIA scores, when controlling for ED symptoms, depression, anxiety and BMI. On step 1, only the EDE-Q scores were entered into the model, R^2= .58, F=173.40, p <.001. On step 2 depression (PHQ-9 score) contributed to the model, R^2= .67, F=33.76, p

<.001. In the final model CES scores also made an additional significant contribution, R^2= .68, F=6.75, p =.011, although the unique variation accounted for was low (1%). Table 3.9 shows the final model for the prediction of the CIA scores by the CES.

Table 3.9 Final model for the prediction of the CIA scores by the Compulsive Exercise Scale

Variable	***ß* (standardised)**	***T***	***P***
Constant		-2.85	.005
EDE-Q	.544	8.90	<.001
PHQ-9	.336	5.79	<.001
CES	.142	2.60	.011
GAD-7	.136	1.70	.092
BMI	.009	.161	.872

Note: BMI = Body Mass Index; EDE-Q = Eating Disorder Examination Questionnaire; GAD-7 = Generalised Anxiety Disorder Assessment-7; PHQ-9 = Patient Health Questionnaire-9; CES = Compulsive Exercise Scale.

3.3.6.4 Application to the competitive sports group

The competitive sports group reported significantly higher scores on the CES (mean= 18.4; SD = 16.72) than those not involved in competitive sport (mean = 6.0, SD = 8.15, Kruskal-Wallis =χ2=31.304, p<.01). For this reason the regression analysis was repeated in the competitive sports group only, in order to test whether the CES would perform better in predicting clinical impairment in a sample with higher compulsive exercise scores. On step 1, only the EDE-Q scores were entered into the model, R^2= .53, F=61.575,

p <.001. In the final model anxiety (GAD score) anxiety made a significant contribution to the model, R^2= .62, F=43.633, p <.001. The CES was unable to account for any unique variance in predicting clinical impairment in this sample. Table 3.10 shows the final model for the prediction of the CIA scores by the CES.

Table 3.10 Final model for the prediction of the CIA scores by the Compulsive Exercise Scale in the competitive sports group

Variable	***ß* (standardised)**	***T***	***P***
Constant		-.661	.511
EDE-Q	.503	4.652	<.001
GAD-7	.379	3.508	.001
CES	.103	.994	.325
PHQ-9	.224	1.94	.059
BMI	.143	1.657	.104

Note: BMI = Body Mass Index; EDE-Q = Eating Disorder Examination Questionnaire; GAD-7 = Generalised Anxiety Disorder Assessment-7; PHQ-9 = Patient Health Questionnaire-9; CES = Compulsive Exercise Scale.

3.3.7 Summary of Study 1 results

- The SS and CES were developed to address the paucity of validated measures of the compulsive nature of weight-loss behaviours in AN. A PCA suggested a one factor structure for both measures, which is in line with the original YFAS scale from which they were developed. Both measures were shown to have good reliability and validity.
- As predicted the competitive sports group showed higher scores in both the SS and CES, although this only reached significance for the CES.
- The SS was able to independently contribute to the prediction of ED symptoms, when controlling for other related measures.
- The CES was unable to uniquely predict ED symptoms directly, but was able to independently contribute to the prediction of clinical impairment when controlling for related measures. This suggests that the presence of compulsive exercise may be predictive of higher levels of ED related clinical impairment.

3.4. Study 2: Ability of the Self-Starvation and Compulsive Exercise Scales in predicting ED symptoms in individuals with experience of Anorexia Nervosa

3.4.1 Study 2: Aims

- To investigate the efficacy of the SS and CES in predicting ED symptoms in individuals with experience of AN (current and past).

3.4.2 Study 2: Hypotheses

- Scores of the SS and CES will be predictive of ED symptoms in individuals with experience of AN (past and current).
- Individuals currently suffering from AN will show higher scores on the SS and CES, as well as other measures of ED symptoms, in comparison to weight restored and recovered individuals.

3.4.3 Study 2: Methods

3.4.3.1 Participants

Seventy-eight participants between the ages of 18-65 were recruited for three experimental groups; individuals currently suffering from AN (AN-C group, n=41), weight restored individuals with experience of AN (AN-WR group, n=18), and individuals fully recovered from AN (AN-R group, n=19). Participants were recruited via email, internet and poster advertisement. This included advertisement on the BEAT website. Additionally, a number of participants were recruited from the ORLA research list of individuals with experience of AN. Participants were required to have a past or current diagnosis of AN to be included in the sample (self-reported). Participants in the AN-C group were required to meet psychological, impairment, and weight criteria for AN, as indexed by self-reported clinical diagnosis, Eating Disorder Examination –Questionnaire (EDE-Q; Fairburn & Beglin, 2008) and Clinical Impairment Assessment (CIA; Bohn & Fairburn, 2008) scores, and Body Mass Index (BMI) respectively to be included in the sample. Participants in the AN-WR group were required to meet psychological and impairment criteria, but were not underweight. Participants in the AN-R group were required to have an EDE-Q score within the normal range (within 1 standard deviation of the community norms) and to have maintained a stable BMI in the healthy range for at least 12 months, and to have had regular menses during this time.

3.4.3.2 Procedure

The research protocol for the recruitment of individuals recovered from AN was reviewed and approved by the University of Oxford's Research Ethics Committee (MSD-IDREC-C1-2013-039 (224); see Appendix 3.1). The research protocol for recruitment of individuals currently suffering with AN was reviewed and approved by the NRES

Committee South Central – Berkshire B (Ref: 13/SC/1370; see Appendix 2.1). The online set of questionnaires was created using the BOS system. Participants were initially sent an information sheet (see Appendix 3.4) and asked some initial screening questions to ensure eligibility for the study. They were then provided with a link to the questionnaire. Consent was provided either online or by means of a consent form emailed to the participant (see Appendix 3.5). The online set of questionnaires consisted of all the measures described in Section 3.3.3.3, plus some additional information (described below).

3.4.3.3. Measures

Participants completed the same questionnaires as described in Section 3.3.3.3.

Other information: Participants provided demographic information (gender, age), as well as the following information:

- Age of onset of anorexia nervosa
- Duration of eating disorder
- Type(s) of treatment received (e.g. inpatient, outpatient, daypatient),
- Lowest BMI (or height and weight if unknown)
- Current BMI (or height and weight if unknown)

3.4.4. Study 2: Demographic Results

Data was collected from 78 participants; 41 had a current diagnosis of AN (AN-C group), 18 were partially recovered from AN, with a healthy weight but remaining psychological symptoms (AN-WR group), and 19 participants fully recovered from AN (AN-R group). All participants in this sample spoke English as a first language. Gender distribution in this sample was 98.7% female (77/78) and 1.3% male (1/78). The majority of participants in this sample were students (56.4%).

In the AN-C group, 25 participants reported inpatient treatment, 37 reported outpatient treatment, and 13 reported day patient treatment. In the AN-WR group 4 participants reported inpatient treatment, 13 reported outpatient treatment, 1 reported day-patient treatment, and 4 reported receiving no treatment. In the AN-R group 5 participants reported inpatient treatment, 13 reported outpatient treatment, 3 reported day patient treatment, and 6 reported receiving no treatment.

Demographic and psychological characteristics of the community sample can be found in Table 3.11. One-Way ANOVAs were used to look at significant differences between the groups, followed by bonferroni corrected post-hoc analysis.

Table 3.11 Demographic and psychological characteristics of the AN sample

	All Participants (N=78)		***AN-C (N=41)***		***AN-WR (N=18)***		***AN-R (N=19)***		***One-Way ANOVA***	***Post Hoc analysis (p<.05)***
Measure	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P-Value**	
Age	27.18	8.48	27.98	10.45	25.78	6.60	26.79	4.50	.646	---
Current BMI	18.12	2.87	15.93	1.53	20.94	1.94	20.18	1.78	<.001	AN-C< AN-WR, AN-R
Lowest BMI	14.06	1.92	13.39	1.76	15.07	1.74	14.79	1.90	.002	AN-C< AN-WR, AN-R
Duration of AN	8.19	8.51	11.51	9.75	2.84	2.69	5.03	3.90	<.000	AN-C>AN-WR, AN-R
Age of Onset	16.79	3.42	16.46	3.73	17.13	2.60	17.31	3.42	.644	---
EDE-Q	3.27	1.55	3.97	1.38	3.73	0.57	1.34	0.70	<.001	AN-R< AN-C, AN-WR
CIA	23.31	14.48	32.54	12.66	19.89	4.92	6.63	4.28	<.001	AN-C>AN-WR>AN-R
YFAS Symptom Count	2.51	1.84	3.02	1.85	2.72	2.05	1.21	0.71	<.001	AN-C, AN-WR> AN-R
YFAS Diagnostic	0.31	0.46	0.46	0.50	0.28	0.46	0.00	0.00	<.001	AN-C> AN-R
CET	14.72	4.75	16.36	4.19	15.45	4.01	10.50	4.13	<.001	AN-C, AN-WR> AN-R

	All Participants (N=78)		*AN-C (N=41)*		*AN-WR (N=18)*		*AN-R (N=19)*		*One-Way ANOVA*	*Post Hoc analysis (p<.05)*
Measure	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P-Value**	
AAQ-II	35.50	10.59	31.44	10.39	35.56	8.22	44.21	7.64	<.001	AN-C, AN-WR< AN-R
GAD-7	10.85	6.50	13.76	6.44	9.44	4.67	5.89	4.57	<.001	AN-C> AN-WR, AN-R
PHQ-9	11.19	7.08	14.41	7.34	10.56	4.45	4.84	3.08	<.001	AN-C, AN-WR> AN-R
LDQ	1.42	4.31	1.07	4.40	3.17	5.77	0.53	0.96	.133	---
SS	40.19	29.89	60.05	24.70	27.89	18.28	9.00	8.60	<.001	AN-C>AN-WR> AN-R
CES	28.85	25.36	41.29	25.84	21.33	20.53	9.11	7.03	<.001	AN-C>AN-WR> AN-R

Note: BMI = Body Mass Index; EDE-Q = Eating Disorder Examination-Questionnaire; CIA = Clinical Impairment Assessment; OxBread = Oxford Brain – Body Research into Eating Disorders Scale; YFAS = Yale Food Addiction Scale; CET = Compulsive Exercise Test; BIS = Barratt Impulsiveness Scale; AAQ-II = Action and Acceptance Questionnaire II; GAD-7 = Generalised Anxiety Disorder Assessment-7; PHQ-9 = Patient Health Questionnaire-9; LDQ = Leeds Dependence Questionnaire; SS= Self-Starvation Scale; CES = Compulsive Exercise Scale.

3.4.5 Study 2 Results: The Self-Starvation Scale (SS)

3.4.5.1 Association between the SS with other self-report measures

As all but 2 of the study variables were not normally distributed (Kolmogorv-Smirnov = $p<.05$), non-parametric Spearman's Rho (*r*) was used to examine the association between the study variables using data from all participants. Significance levels were corrected for multiple comparisons.

As shown in Table 3.12 the SS scores were significantly related to measures of ED symptoms (EDE-Q, and CIA), compulsive exercise (CET), experiential avoidance (AAQ-II), BMI, depression (PHQ-9) and anxiety (GAD-7). This relationship was in a positive direction for ED symptoms and clinical impairment, compulsive exercise, depression and anxiety, and in a negative direction for experiential avoidance and BMI.

Again the SS was found to significantly correlate with food addiction (YFAS: $r = .41$). However, the correlation became negative when removing those who reported bulimic episodes (n=30) ($r = -.63$).

Table 3.12 Correlations of the Self-Starvation Scale with self-reported ED symptoms and clinical impairment, experiential avoidance, BMI, depression and anxiety.

Spearman's Rho	*SDQ*	*EDE-Q*	*CIA*	*CET*	*AAQ-II*	*BMI*	*PHQ-9*	*GAD-7*
SS	1.00	**.838***	**.852***	**.471***	**-.552***	**-.644***	**.688***	**.596***
EDE-Q		1.00	**.874***	**.593***	**-.694***	**-.394***	**.760***	**.638***
CIA			1.00	**.567***	**-.679***	**-.555***	**.789***	**.755***
CET				1.00	**-.361***	-.219	**.435***	**.367***
AAQ-II					1.00	.309	**-.778***	**-.778***
BMI						1.00	**-.374***	**-.436***
PHQ-9							1.00	**.795***
GAD-7								1.00

Note: BMI = Body Mass Index; EDE-Q = Eating Disorder Examination-Questionnaire; CIA = Clinical Impairment Assessment; CET = Compulsive Exercise Test; AAQ-II = Action and Acceptance Questionnaire II; GAD-7 = Generalised Anxiety Disorder Assessment-7; PHQ-9 = Patient Health Questionnaire-9; SS = Self-Starvation Scale.

* $p<.05$ (corrected for multiple comparisons)

3.4.5.2 Does the SS predict ED symptoms in individuals with past or present experience of AN

The AN-C group showed higher scores on the SS (mean = 60.1, SD=24.7), than the AN-WR (mean = 27.9, SD=18.3), and AN-R (mean = 9.0, SD=8.6). These differences were found to be significant (Kruskal-Wallis (χ2=45.35 p<.000)). Post-hoc pairwise comparison showed that these differences were significant between each group (see Table 3.13).

Table 3.13. Pairwise comparisons of Self-Starvation Scale scores between groups

	AN-C	**AN-WR**	**AN-R**
AN-C	----	----	----
AN-WR	*U*=623.0, p=<.001	----	----
AN-R	*U*=761.5, p=<.001	*U*=290.5, p=<.001	----

Hierarchical regression was used to assess the ability of the SS to predict EDE-Q scores in all participants. As the EDE-Q scores significantly correlated with scores on the CIA, CET, AAQ, GAD-7, PHQ-9 and BMI, these variables were added as covariates in step 1. On step 1, scores on the CIA, CET, AAQ and BMI produced a significant model, R^2= .79, *F*=45.63, *p* <.001. In the final model, it was shown that the SS made additional significant contributions to the model, R^2 = .84, *F*= 20.17, *p*= <.001, accounting for an extra 5% of the variance (final model shown in Table 3.14). The GAD-7 and PHQ-9 scores were not able to explain variance in the EDE-Q scores.

Table 3.14 Final model for the prediction of the EDE-Q scores by the Self-Starvation Scale.

Variable	ß (standardised)	*T*	*p*
Constant		-0.303	.793
SS	.469	4.491	<.001
CIA	.375	2.806	.006
BMI	.225	3.642	.001
CET	.178	3.054	.003
AAQ-II	-.229	-2.841	.006
PHQ-9	.013	.125	.901
GAD-7	-.093	-1.016	.313

Note: BMI = Body Mass Index; CIA = Clinical Impairment Assessment; CET = Compulsive Exercise Test; AAQ-II = Action and Acceptance Questionnaire II; GAD-7 = Generalised Anxiety Disorder Assessment-7; PHQ-9 = Patient Health Questionnaire-9; SS = Self-Starvation Scale

When looking at the Restraint subscale scores of the EDE-Q, the SS was able to account for a larger amount of unique variance in comparison to the global EDE-Q scores. The CIA, CET, AAQ-II, PHQ-9, GAD-7 and BMI were again entered in the first block. Only the CIA scores was a significant predictor of Restraint subscale scores in the first model, R^2= .63, F=20.02, p <.001. The addition of the SS in the second block was able to account for an extra 7% of the unique variance in these scores, R^2= .70, F=17.33, p= .001 (final model shown in Table 3.15). The AAQ-II and CET were also significant predictors in the final model.

Table 3.15 Hierarchical regression model for the prediction of the EDE-Q Restraint subscale scores by the Self-Starvation Scale

Variable	ß (standardised)	*T*	*p*
Constant		1.119	.267
SS	.594	4.163	<.001
CIA	.093	.510	.612
BMI	.037	.445	.658
CET	.172	2.159	.034
AAQ-II	-.234	-2.124	.037
PHQ-9	-.007	-.052	.959
GAD-7	-.091	-.736	.464

Note: BMI = Body Mass Index; CIA = Clinical Impairment Assessment; CET = Compulsive Exercise Test; AAQ-II = Action and Acceptance Questionnaire II; GAD-7 = Generalised Anxiety Disorder Assessment-7; PHQ-9 = Patient Health Questionnaire-9; SS = Self-Starvation Scale

The ability of the SS to predict scores on the EDE-Q was particularly pronounced in the AN-C group. It was able to account for an extra 11% variance in the global EDE-Q scores (see Table 3.16) , and an extra 10% of variance in the EDE-Q Restraint subscale scores (See Table 3.16), whilst controlling for the variance associated with the CIA, CET, AAQ, GAD-7, PHQ-9 and BMI.

Table 3.16 Hierarchical regression model for the prediction of the EDE-Q Global scores and Restraint subscale scores by the Self-Starvation Scale in the AN-C group

Variable	R^2 Change	ß (standardised)	T	p
EDE-Q Global	.106			
Constant			0.020	.984
SDQ		.591	4.958	<.001
CIA		-.018	-.107	.916
BMI		.202	2.716	.010
CET		-.069	-.873	.389
AAQ-II		-.280	-2.781	.009
PHQ-9		.108	.840	.407
GAD-7		.143	1.134	.265
EDE-Q Restraint	.104			
Constant			0.298	.768
SDQ		.583	2.798	.009
CIA		-.035	-.121	.905
BMI		.128	.989	.330
CET		-.035	-.256	.799
AAQ-II		-.195	-1.109	.275
PHQ-9		.086	.383	.705
GAD-7		.026	.118	.906

Note: BMI = Body Mass Index; CIA = Clinical Impairment Assessment; CET = Compulsive Exercise Test; AAQ-II = Action and Acceptance Questionnaire II; GAD-7 = Generalised Anxiety Disorder Assessment-7; PHQ-9 = Patient Health Questionnaire-9; SS = Self-Starvation Scale

3.4.6 Study 2 Results: The Compulsive Exercise Scale (CES)

3.4.6.1. The association between the CES and other self-report measures

As shown in Table 3.17 the CES scores were significantly related to measures of ED symptoms (EDE-Q and CIA), compulsive exercise (CET), experiential avoidance (AAQ-II), BMI, depression (PHQ-9) and anxiety (GAD-7).

This relationship was in a positive direction for ED symptoms and clinical impairment, compulsive exercise, depression and anxiety, and in a negative direction for experiential avoidance and BMI.

Table 3.17 Correlations of the Compulsive Exercise Scale with self-reported ED symptoms and clinical impairment, experiential avoidance, BMI, depression and anxiety.

Spearman's Rho	*CES*	*EDE-Q*	*CIA*	*CET*	*AAQ-II*	*BMI*	*PHQ-9*	*GAD-7*
CES	1.00	**.570***	**.614***	**.744***	**-.456***	**-.414***	**.512***	**.522***
EDE-Q		1.00	**.874***	**.593***	**-.694***	**-.394***	**.760***	**.638***
CIA			1.00	**.567***	**-.679***	**-.555***	**.789***	**.755***
CET				1.00	**-.361***	-.219	**.435***	**.367***
AAQ-II					1.00	.309	**-.778***	**-.778***
BMI						1.00	**-.374***	**-.436***
PHQ-9							1.00	**.795***
GAD-7								1.00

Note: BMI = Body Mass Index; EDE-Q = Eating Disorder Examination-Questionnaire; CIA = Clinical Impairment Assessment; CET = Compulsive Exercise Test; AAQ-II = Action and Acceptance Questionnaire II; GAD-7 = Generalised Anxiety Disorder Assessment-7; PHQ-9 = Patient Health Questionnaire-9; CES = Compulsive Exercise Scale.

* $p<.05$ (corrected for multiple comparisons)

3.4.6.2. Does the CES predict ED symptoms in individuals with past or present experience of AN

The AN-C group showed higher scores on the CES (mean = 41.3, SD=25.8), than the AN-WR (mean = 21.3, SD=20.5), and AN-R (mean = 9.1, SD=7.0). The difference between the group means was found to be significant (Kruskal-Wallis (χ2=26.25 p<.000)). Post-hoc pairwise comparison showed that the difference between the AN-C with both the AN-R and AN-WR group was significant. However the difference was not significant between the AN-WR and AN-R groups (see Table 3.18).

Table 3.18 Pairwise comparisons of Compulsive Exercise Scale scores between groups

	AN-C	**AN-WR**	**AN-R**
AN-C	----	----	----
AN-WR	*U*=548.0, p=.003	----	----
AN-R	*U*=694.0, p=<.001	*U*=230.5, p=.070	----

Hierarchical regression analysis was used to assess the ability of the CES to predict ED symptoms. The CES was unable to account for any unique variance in predicting either the EDE-Q or CIA scores, when controlling for the variance associated with other measures of ED symptoms, experiential avoidance, BMI, depression or anxiety.

3.4.7 Summary of Study 2 results

- As predicted, scores on the SS and CES were significantly higher in those currently suffering from AN, although scores on the SS were also significantly higher in weight-restored compared to recovered AN participants.
- The SS was able to independently predict ED symptoms when controlling for other related measures, and this predictive ability was highest for the Restraint subscale of the EDE-Q. This relationship was particularly strong when looking at the AN-C group in isolation.
- The CES was unable to independently predict ED symptoms in this sample, and did not show the predictive relationship with clinical impairment that was shown in Study 1.
- These findings suggest that the ability of the SS to predict ED symptoms is highest when used in current AN sufferers, and is a stronger measure than the CES when used in a clinical sample.

3.5 Discussion

3.5.1 Can the concept of dependence be used to capture compulsive weight-loss behaviours?

The main aim of Study 1 was to develop useful measures of the compulsive weight-loss behaviour seen in AN. To this end a 16-item SS and 15-item CES were developed and validated in a community sample. These measures were developed by adapting the questions from the YFAS (Gearhardt et al., 2009), in which the DSM-IV criteria for substance dependence are used to determine addiction to food, to fit the constructs of self-starvation and compulsive exercise in AN. Participant feedback suggested that the dichotomous questionnaire items did not optimally capture behaviour in these measures. Thus, only the likert scale items were analysed and dichotomous items indexing diagnostic criteria were omitted. This reflects the current move away from the use of diagnoses in understanding psychopathology (Insel et al., 2010), and supports the notion of using compulsivity as a construct evident across disorders (Robbins et al., 2012).

The results of a PCA suggested a one factor structure for both measures, which is reflective of the one factor structure of the YFAS. Both measures were shown to have good criterion-related validity, internal consistency and test-retest reliability. The one factor structure suggested for the SS, the CES, and the YFAS may support the notion that compulsive behaviour, captured using the criteria for dependence, is a common underlying construct across these disorders.

The SS correlated significantly with measures of ED symptoms, impairment and excessive exercise. When controlling for clinical impairment, depression, anxiety and BMI, the SS scores emerged as a significant independent predictor of ED symptoms in a regression analysis, accounting for unique variance in EDE-Q scores. This suggests that

adapting the concept of dependence for self-starvation behaviour may be a useful way of capturing ED related behaviour, and supports increasing suggestion that compulsive weight-loss behaviour in AN and other EDs can be compared to the compulsive drug-seeking behaviour seen in dependence disorders (Barbarich-Marsteller et al., 2011; Kaye, Wierenga, Bailer, Simmons, Wagner, et al., 2013; Walsh, 2013; Zink & Weinberger, 2010). Depression, anxiety and BMI did not emerge as significant predictors of ED symptoms, disputing previous suggestions that comorbid anxiety and depressive symptoms may contribute to results in ED research, and even to the development of the disorder (Corcos et al., 2000; Pollice et al., 1997; Strober, 2004).

The CES was unable to significantly predict ED symptoms in the community sample, and did not correlate significantly with EDE-Q scores. This may reflect the fact that compulsive exercise can occur independently of ED symptoms (Berczik et al., 2012; De Coverley Veale, 1987). However, as the CES scores did significantly correlate with CIA scores, the ability of the CES to predict ED-related impairment was assessed using regression analysis. The EDE-Q scores and depression were significant predictors of clinical impairment, and the CES scores also emerged as an independent predictor of impairment. These results suggest that the presence of depressive symptoms and compulsive exercise may contribute to higher levels of ED-related clinical impairment, supporting studies showing that both depression and compulsive exercise are associated with poor prognosis in AN (Bryant-Waugh, Knibbs, Fosson, Kaminski, & Lask, 1988; Herpertz-Dahlmann, Wewetzer, & Remschmidt, 1995; Solenberger, 2001). Compulsive exercise in EDs is also associated with higher levels of body dissatisfaction (Brewerton, Stellefson, Hibbs, Hodges, & Cochrane, 1995), anxiety and depression (Meyer et al., 2011), lower minimum BMI (Shroff et al., 2006), greater persistence of symptoms, and

higher levels of relapse (Carter et al., 2004), further supporting the notion that the presence of compulsive exercise may lead to high levels of ED-related impairment.

As predicted the individuals involved in competitive sports showed higher scores on both the SS and the CES, although this only reached significance for the CES. This non-significant result for the SS scores is surprising considering previous studies which have shown higher levels of ED symptoms in athletes (Martinsen & Sundgot-Borgen, 2013; Sundgot-Borgen & Torstveit, 2004). However, this may reflect the fact that the current study only required individuals to be involved in a competitive sport, in comparison to other studies which have used elite professional athletes. Elite athletes are shown to have psychological traits that are also associated with EDs, such as obsessive-compulsive tendencies, perfectionism, and a high drive for achievement (Forsberg & Lock, 2006; Thompson & Sherman, 1999), which may not be as evident at a non-professional level. Furthermore, some professional sports emphasise a reduction in body mass, and athletes taking part in these sports are considered at increased risk for EDs (Rodriguez, Di Marco, & Langley, 2009), whereas low body weight is unlikely to be enforced in non-professional competitive sports.

Scores on the SS and CES were found to correlate significantly with scores of food addiction (the YFAS) in the community sample. However, when removing participants who reported binge-eating episodes, this correlation disappeared. The SS also correlated with the YFAS in the AN sample, but this correlation became negative when removing those who reported bulimic episodes. This result suggests that those who engage in binge/purge behaviours are less likely to display the rigid and controlled self-starvation behaviours captured by the SS, and supports suggestion of a specific relationship between binging and addictive-like behaviours (Corsica & Pelchat, 2010; Davis & Carter, 2009; Gearhardt et al., 2009).

These results suggest that the SS may be a useful measure of compulsive self-starvation, and effective in predicting ED symptoms directly in a community sample, whereas the CES appears to be a better predictor of the clinical impairment associated with the presence of compulsive exercise. The efficacy of using measures adapted from dependence criteria in capturing compulsive weight-loss behaviour supports the notion of an underlying compulsive nature of behaviour across disorders such as AN, food addiction, and substance dependence.

3.5.2 The ability of the SS and CES in predicting symptoms in individuals with experience of Anorexia Nervosa.

In order to further investigate the efficacy of the SS and CES in capturing compulsive weight-loss behaviour, the ability of these measures in predicting ED symptoms and clinical impairment was investigated in a sample of individuals with current and past AN. As predicted, the scores on both measures were significantly higher in the currently ill AN group, in comparison to the weight restored and recovered AN groups. The scores on the SS were also significantly higher in the weight restored AN group in comparison to the recovered AN group, which is likely reflective of the higher ED symptoms remaining in the weight restored group.

The SS was able to account for unique variance in predicting ED symptoms in the AN sample when controlling for clinical impairment, compulsive exercise, experiential avoidance, depression, anxiety and BMI, variables which significantly correlated with ED symptoms. The predictive ability of the SS was particularly pronounced when looking at the Restraint subscale of the EDE-Q. This subscale is centred on the rigid control of eating behaviour seen in EDs, and thus this result is likely to reflect the compulsive and rule driven nature of self-starvation measured by the SS. The predictive ability of the SS was also more

pronounced in the current AN group, suggesting this measure may be particularly useful in clinical samples, in which extreme self-starvation behaviour is likely to be more evident. The SS also correlated more highly with BMI than existing measures of ED symptoms, indicating that higher levels of the compulsive self-starvation behaviour in AN captured by this measure may be a better indicator of a tendency towards a lower BMI than these existing measures.

Although scores on the CES significantly correlated with ED symptoms and clinical impairment, it was unable to independently predict either of these constructs in the AN sample when controlling for other measures of ED symptoms, experiential avoidance, BMI, depression or anxiety. This further supports the notion that compulsive exercise may be present in the absence of disordered eating, and may be independent of AN status in this sample. Excessive exercise in AN often persists into recovery (Kron, Katz, Gorzynski, & Weiner, 1978), and this finding may indicate the presence of compulsive exercise behaviour in recovered individuals who no longer show elevated levels of ED symptoms. The predictive relationship found between the CES and clinical impairment found in the community sample was also not evident in the AN sample. This may reflect the fact that clinical impairment is likely to be higher in the AN sample irrespective of the presence of compulsive exercise. However, the presence of compulsive exercise may be related to higher levels of clinical impairment when in conjunction with the subclinical ED symptoms found in the community sample.

3.5.3 Limitations

The development of the SS and CES was motivated by increased theoretical suggestion of parallels between compulsive behaviour in AN and substance dependence, and the face validity of this concept shown in the qualitative reports of those with AN

reported in Chapter 2. Further development of these measures and would benefit from the input of individuals with AN to ensure the measures adequately capture the compulsive nature of weight loss behaviour in AN.

Both studies relied on self-report, both in terms of the self-report measures used, and reporting of past or current diagnoses of AN. This reliance on self-report may have led to inaccurate responses. This may be particularly relevant for individuals with AN, who have been shown to have low interoceptive awareness (Fassino et al., 2004). Whilst the EDE-Q has been shown to be effective when used in the place of interviewer-based assessment, future research may benefit from the use of interview assessment in determining samples. In addition, both studies used a cross sectional design, meaning causal inferences cannot be deduced from the results. Longitudinal research would allow further investigation of the role of compulsive weight loss behaviour in the development and maintenance of AN.

The community sample was largely made up of a student population, and as such the results may not be generalisable to the wider population. In addition, the AN sample was largely female, making the results less generalisable to males with AN. The addition of the competitive sports group in the community sample may be seen as a confound in validating the measures, due to reports of higher levels of ED symptoms in athletes (Martinsen & Sundgot-Borgen, 2013; Sundgot-Borgen & Torstveit, 2004), however this group did not significantly differ to the healthy control group on any measures other than the CEQ and CET measures of compulsive exercise.

3.5.4 Conclusions

The results of this study further augment the qualitative parallels between AN and SUDs reported in Chapter 2, and support the utility of using the criteria for substance dependence to capture compulsive weight-loss behaviour in AN. Furthermore, these results indicate that compulsivity as a construct of behaviour may have transdiagnostic application, on which disorder-specific themes are superimposed. The SS appears to be stronger measure of ED-specific compulsive behaviour, whereas compulsive exercise, as measured by the CES, may be relevant to a wider population. Research examining compulsivity in AN is lacking, and both investigation of the role of compulsive behaviour in the maintenance of AN, and experimental studies looking at behavioural and neural correlates of this construct are required.

4. Habit formation in Anorexia Nervosa: An experimental investigation.

4.1 Overview

As Chapters 2 and 3 have discussed, aspects of the compulsive behaviours characteristic of AN have increasingly been compared to the compulsive nature of maladaptive behaviours in both OCD, and substance dependence. Chapter 2 showed how the subjective experience of compulsive weight-loss behaviour in AN may be comparable to the DSM-V criteria for SUDs. This was further supported by Chapter 3, in which two novel measures of compulsive behaviour in AN were developed and validated by adapting a measure of food addiction derived from the DSM-IV criteria for substance dependence. To further investigate the transdiagnostic significance of compulsive behaviour in AN, the behavioural mechanisms underpinning this behaviour must be explored. As excessive habit formation has been suggested to underpin compulsive behaviour in OCD and substance dependence, this chapter will explore this possibility in AN by addressing the following questions:

- Do individuals with experience of AN (current and past) show a generalised tendency towards developing habits in learning, similar to that seen in OCD and substance dependence?
- Is a tendency to develop habits trait-related, evidenced by a tendency towards habitual behaviour in both acute and recovered AN participants?
- Is a tendency towards habit formation specific to appetitive (pursuit of reward) or avoidant (avoidance of something aversive) stimulus-response contingencies in AN?

4.2 Background

Chapter 2 investigated the importance of compulsive behaviour in the development and maintenance of AN, from the perspective of the individual, and provided preliminary support for parallels with the DSM-V criteria for SUDs. A feeling of impaired control, and an inability to disengage from compulsive behaviours described by participants in this study supports recent theoretical accounts of the role of persistent maladaptive habits in AN. These results suggested that the compulsive nature of weight-loss behaviour in AN is an important feature of AN, and may be key in the persistence of the disorder. This was further supported in Chapter 3, in which two novel measures of compulsive behaviour in AN, modelled on addiction criteria, were validated and shown to be independently predictive of ED symptoms and clinical impairment. This would suggest that the elements of behaviour captured by the criteria for addiction, can also be used to capture the compulsive nature of weight-loss behaviour in AN.

As discussed in Section 1.9, emergent evidence suggests that dysregulation of the balance between the goal-directed and habitual systems of behavioural control may provide a mechanism by which the development of well-entrenched, compulsive behaviours can occur across disorders. Section 1.12 introduced the RDoC Reasearch Domain Criteria, of which compulsive behaviour is currently included as a behavioural manifestation of 'Habit' in the RDoC framework. A shift in balance away from goal-directed control and towards excessive habit learning has been shown in OCD, substance dependence, and in obese individuals with BED (Gillan et al., 2015; Gillan et al., 2013; Gillan et al., 2011; Sjoerds et al., 2013; Voon et al., 2014), suggesting a common behavioural underpinning for the persistence of behaviour across disorders of

compulsivity, and may provide a potential underpinning for the compulsive and persistent nature of behaviour in AN (Steinglass & Walsh, 2006; Walsh, 2013).

As discussed in Section 1.9, cortico-striatal connectivity has been associated with the tendency to rely on habits, and aberrancies in the function and structure of both cortical and striatal regions have been reported in AN (Cowdrey et al., 2011; Favaro, Tenconi, Degortes, Manara, & Santonastaso, 2014; Frank et al., 2012; Frank et al., 2013; Uher et al., 2004; Wagner et al., 2007). Further support for the involvement of habitual control of behaviour in AN comes from an fMRI study by Rothemund et al (2011), in which high levels of self-reported compulsivity predicted deactivation of the fronto-striatal circuitry. Whilst viewing high calorie pictures, severely low weight AN patients showed increased activation in the caudate and precuneus, regions involved in automatic habit learning processes. Additionally, areas involved in the goal-directed control of behaviour, the OFC and middle and superior frontal gyrus, were found to have reduced grey matter volume in these patients (Rothemund et al., 2011). Furthermore, restrictive food choice in AN has been associated with activity in the caudate, which may reflect the formation of disorder-related habits (Steinglass, Foerde, Kostro, Shohamy, & Walsh, 2015). Whilst this provides preliminary evidence that the neurocircuitry associated with goal-directed actions and habits are aberrant in AN, it does not directly link this to behavioural learning processes. This chapter aims to investigate this more directly in AN, with two tasks that measure the development and persistence of stimulus-response habits.

Despite providing preliminary evidence for parallels between compulsive behaviour in AN and substance dependence, Chapters 2 and 3 are limited by their reliance on self-report. This reliance on self-report may have led to inaccurate responses, both in the reporting the subjective experience of compulsivity, and in responses to questionnaires. This may be particularly relevant for individuals with AN, who have been shown to have

low interoceptive awareness (Fassino et al., 2004). Using validated behavioural tasks will allow investigation of neuropsychological processes involved in compulsive behaviour in AN, independent of subjective reports. The tasks used in this chapter have been previously employed to assess the balance between goal-directed and habitual control of behaviour, and have been shown to activate neural regions associated with goal-directed and habitual control of behaviour (Gillan et al., 2015; Sjoerds et al., 2013).

The tendency to develop habits in learning was investigated in individuals both currently ill and recovered from AN, and healthy controls, using two validated outcome-devaluation tasks, previously used to investigate a reliance on habits in OCD (Gillan et al., 2015; Gillan et al., 2013; Gillan et al., 2011), and substance dependence (Sjoerds et al., 2013). The outcome devaluation paradigm is included as a measure of the 'Habit' construct of the RDoC. In this paradigm previously rewarded action-outcome contingences are devalued (no longer rewarded), and the persistence of the response behaviour despite this devaluation is measured as an indication of habit formation. The tasks used in this study allowed the investigation of the persistence of both appetitive (based on the pursuit of a rewarding outcome) and avoidance (based on the avoidance of an aversive outcome) habits in individuals with experience of AN. Using both individuals with a current diagnosis of AN, and those recovered from AN will allow the investigation of habit formation as either state-related (i.e. due to the effects of starvation in acute AN), or trait-related (i.e. still present in individuals after recovery).

4.3 Aims

- To assess whether a generalised reliance on habits in learning is evident in AN.
- To determine whether there are differences in a tendency towards developing appetitive and avoidance habits in AN.
- To investigate whether a tendency towards relying on habits is a state or trait-related phenomena by investigating this in acute and recovered AN.

4.4 Hypotheses

- It is hypothesised that individuals with experience of AN (both current and past) will show enhanced habit formation in two outcome devaluation tasks, evidenced by a persistence of previously learned, but subsequently devalued stimulus-response actions.

4.5 Methods

4.5.1 Participants

Forty-four participants were recruited for three experimental groups; current AN (AN-C, n=13), recovered AN (AN-R, n=14), and healthy controls (HC, n=17). General exclusion criteria included age <18 or >60, insufficient English language skills, and male sex. The specific inclusion and exclusion criteria outlined below was designed to enable valid differentiation between the AN groups and the healthy controls. Ethical permission for this study was obtained from the NRES South Central – Oxford A Research Ethics Committee (see Appendix 4.1).

AN-C Group

Inclusion criteria for the AN-C group included a current diagnosis of *restrictive* AN according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), as indexed by the Structured Clinical Interview for DSM-IV (SCID), the Eating Disorder Examination (EDE), and current BMI. Participants with a history of, or current diagnosis of binge/purge type AN or BN were excluded. Four participants were on both antidepressant (SSRI or SNRI) and atypical antipsychotic medication, and two were taking antidepressant (SSRI) medication only. Seven participants currently met the criteria for a mood disorder, seven met the criteria for current Generalised Anxiety Disorder (GAD), and two met the criteria for current OCD. Three participants reported previous but not current episodes of depression, and one participant reported a previous episode of PTSD. One participant was excluded after screening due to a history of binge/purge AN.

AN-R Group

Inclusion criteria for the AN-R group included a past diagnosis of *restrictive* AN according to the DSM-IV as assessed by the SCID. Participants with a history of binge/purge type AN or BN were excluded. In addition, participants must have maintained a BMI between 18.5 and 25 for the previous 12 months (assessed by self-report), score within 1 SD of the EDE and EDE-Q global mean scores for young women, and not meet current criteria for any DSM-IV disorder. Whilst none of the AN-R participants currently met criteria for depression, twelve had previously met the criteria for depression, and five were currently taking antidepressant medication. In addition, three participants had previously met the criteria for GAD, and one for OCD. One participant was excluded after screening due to a history of BN.

HC Group

Inclusion criteria for the HC group included a current BMI between 18.5 and 25, no first degree relative with a current or past ED diagnosis (assessed by self-report), no current or past diagnosis of a DSM-IV disorder, and scores within 1 SD of the EDE and EDE-Q mean scores for young women. Four participants were excluded after screening due to violation of one of the above criteria.

4.5.2 Procedures

Participants were initially sent an information sheet (see Appendix 4.2) and description of the study by email. They were then asked to complete a number of screening questions, and an online version of the EDE-Q to ensure they met the criteria for the study. Participants were then invited to an initial screening session at the Warneford Hospital. After informed consent was taken (see Appendix 4.3), participants were screened for

current DSM-IV Axis-I disorders using the SCID, and ED symptoms using the EDE. Verbal IQ was assessed using the National Reading Test (Nelson & Willison, 1991). Participants were also given a battery of questionnaires to complete (described below), and height and weight were taken to calculate BMI. Participants subsequently attended one or two more sessions to complete the two outcome devaluation tasks. To assess subjective state prior to the tasks, participants completed a number of 100mm VAS scales measuring mood (happiness, despondence, anxiety), appetite (hunger, thirst, desire to eat and fullness), and ED-related variables (feeling of fatness, fear of fatness). VAS scales were anchored from at 'not at all', to 'extremely' (see Appendix 4.4). To reduce order effects, the two tasks were counterbalanced across participants. Following completion of the study, participants were paid £7.50 per hour in compensation for their time.

4.5.3 Measures

Eating Disorder Examination – Questionnaire (EDE-Q): (Fairburn & Beglin, 2008) See Section 2.3.3 and Appendix 2.4.

Clinical Impairment Assessment (CIA): (Bohn & Fairburn, 2008) See Section 2.3.3 and Appendix 2.5.

Barratt Impulsiveness Scale (BIS): (Patton et al., 1995) See Section 2.3.3 and Appendix 3.13.

Action and Acceptance Questionnaire (AAQ): (Bond et al., 2011) See Section 3.3.3.3 and Appendix 3.10.

National Reading Test (NART): The NART-R (Nelson & Willison, 1991) contains 50 irregular words (see Appendix 4.5). For each word, participants are asked to pronounce the

word and each response is marked as correct or incorrect by the researcher. Using the number of words pronounced correctly, a score of IQ can be calculated.

Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ): The SPSRQ (Torrubia, Avila, Molto, & Grande, 1995) is a 48-item self-report questionnaire (see Appendix 4.6) designed to measure the Behavioural Inhibition System (BIS), and Behavioural Approach System (BAS), motivational systems of punishment and reward. Twenty-four items relate to sensitivity to punishment, and 24 relate to sensitivity to reward. The questionnaire is scored by giving a 'yes' response and score of 1, and a 'no' response a score of 0. Scores are summed for the reward and punishment items separately. This measure has been shown to have good internal consistency of the scales, validity, and test-retest reliability (Torrubia, Ávila, Moltó, & Caseras, 2001; Torrubia et al., 1995).

Beck Depression Inventory (BDI): The BDI-II (Beck, Steer, & Brown, 1996) is a validated 21-item self-report questionnaire, which measures depressive symptom severity in the past two weeks (see Appendix 4.7). Participants rate their answers using a 0 to 3 scale with higher scores indicating greater depression severity (range 0 to 63). The standard cut offs used are as follows: 0 to 13, minimal depression; 14 to 19, mild depression; 20 to 28, moderate depression; and 29 to 63, severe depression (Beck, Steer, Ball, & Ranieri, 1996).

State Trait Anxiety Scale (STAI): The STAI (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) is a 40-item self-report questionnaire that measures state anxiety (STAI-S) and trait anxiety (STAI-T; see Appendix 4.8). Items are scored from 0 (*not at all*) to 3 (*a lot*). The STAI has good reliability and discriminate validity has a good internal consistency (between 0.90 and 0.93 for the STAI-S and between 0.84 and 0.87 for the

STAI-T). The convergent validity with respect to other measures of anxiety ranges from 0.73 to 0.85 (Spielberger et al., 1983).

Obsessive-Compulsive Inventory - revised (OCI-R): The OCI-R (Foa et al., 2002) is an 18-item self-report questionnaire designed to determine the severity of OCD symptoms (see Appendix 4.9), and is a shorter revised version of the original OCI (Foa, Kozak, Salkovskis, Coles, & Amir, 1998). Items are scored from 0 (*not at all*) to 4 (*extremely)*. The OCI-R shows good internal consistency (between 0.81 and 0.93), and good convergent validity with the original OCI (0.90) and with other measures of measures of obsessive-compulsive symptoms (between 0.53 and 0.85) (Foa et al., 2002).

Yale Brown Cornell Eating Disorder Scale Self-Report Questionnaire (YBC-EDs-SRQ): The YBC-EDs-SRQ (Bellace et al., 2012) is a self-report questionnaire (see Appendix 4.10) modelled on the original Yale-Brown-Cornell Eating Disorder Scale (YBC-EDs), a semi-structured interview assessing core preoccupations and rituals related to eating disorders (Mazure, Halmi, Sunday, Romano, & Einhorn, 1994). It consists of a 65-item symptom checklist, followed by 19 questions. The 19 questions are scored on a 5 point scale from 0 (none/not present) to 4 (extreme), with descriptions corresponding to each scale point. The YBC-EDs-SRQ shows good convergent validity with the orginal YBC-EDS (between 0.60 and 0.75), and test-retest reliability (between 0.65 and 0.94) (Bellace et al., 2012).

Self-Starvation Scale (SS): The SS (Godier & Park, 2014), is a 17-item self-report questionnaire that captures the compulsive element of self-starvation in EDs (see Appendix 3.6). Items are scored on a 7 point likert scale in which participants indicate the number of days out of 28 in which the statement has applied to them, ranging from 0 (Never) to 6 (Everyday). See Chapter 3 for development and validation of this measure.

4.5.4 Outcome Devaluation tasks

4.5.4.1 Noise Avoidance Paradigm

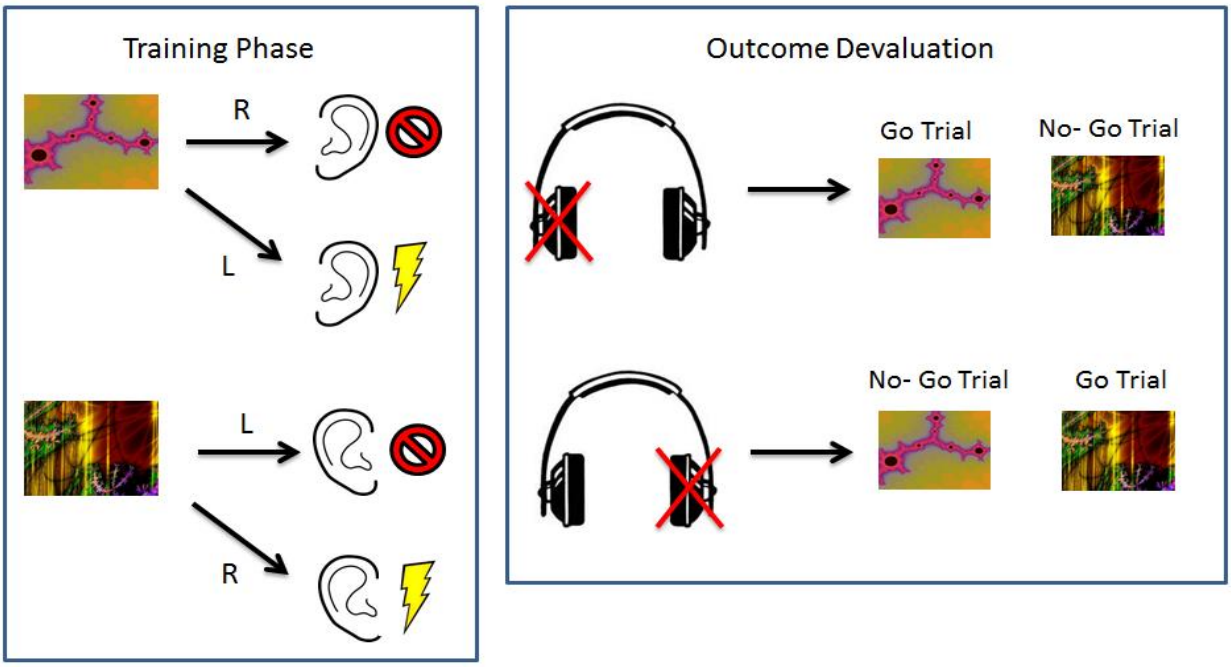
Avoidance habits were assessed using the Noise Avoidance Paradigm, an adapted version of a shock avoidance task used by Gillan et al (2013, 2015) in patients with OCD. The computerised noise avoidance task requires participants to respond to warning stimuli to avoid hearing an unpleasant noise in either their left or right ear. Prior to beginning the task, participants set the volume of the noise themselves, and were instructed to set it to a volume to a level that was unpleasant, but not painful. Participants were then asked to rate the noise unpleasantness using a VAS scale. The conditioned stimuli (CS) were two coloured rectangles presented for 750ms. These stimuli predict an unpleasant noise in either the left or right ear. To avoid hearing the unpleasant noise, participants were required to make a left or right keyboard response whilst the stimuli appear on the screen. The left response avoids the noise in the left ear, and the right response avoids the noise in the right ear (See Figure 4.1, Training Phase). The unpleasant noise was played when the participant pressed the incorrect key or failed to respond within the 750ms that the stimulus is on screen. Presentation of the stimuli order was randomised, and rectangle colour was counterbalanced across participants. Participants were informed that their task throughout the entire experiment was to avoid receiving the unpleasant noises. Participants were first shown stimulus-outcome contingencies and then instructed that they could avoid unpleasant noises by performing the correct avoidance response while the stimulus was still on screen. There were 6 practice trials before the real task begins.

The main task design consisted of four stages: a brief training session (6 trials per CS), a devaluation test in extinction (12 trials per CS) (devaluation sensitivity test), an extended training session (60 trials per CS), and a final devaluation test in extinction (12

trials per CS) (habit test). Unpleasant noise outcomes were devalued by disconnecting the headphone from one of the ears in full view of the participants (See Figure 4.1, Outcome Devaluation). The headphone attached to the other ear remained connected and was thus still valued. Participants were informed that they would no longer hear the unpleasant noise in the disconnected ear and their only task was to avoid receiving the remaining noise. Devaluation was conducted in extinction to control for additional reinforcement learning. Participants behaving in a goal-directed manner should not respond to the CS that predicts the devalued outcome, but should maintain responding to avoid the valued outcome. In the habit test, the alternate ear to that devalued during the devaluation sensitivity test was then devalued. The devaluation procedure was counterbalanced across participants for left and right ears. Half of the participants had their left ear devalued first, and the other half had their right ear devalued first.

Following the behavioural experiment, participants were tested on their explicit knowledge of stimulus-action-outcome associations learned during training. Participants also retrospectively rated VAS scales from 0 to 100 probing 1) their level of expectancy that a shock would follow the devalued CS; 2) the extent to which they experienced an urge to continue responding in spite of the devaluation; and 3) the extent to which they actively attempted to suppress this urge during the extinction test. Finally, participants were asked to report why they continued to respond in the habit test or felt compelled to continue do so, even if they did not actually respond.

Figure 4.1 Training and outcome devaluation stages of the Noise Avoidance Paradigm



4.5.4.2 The Slips-of-Action Paradigm

A validated shortened and adapted version of the 'Fabulous Fruit Task' designed to investigate the balance between goal-directed behaviour and habit learning was used to measure appetitive habit formation (de Wit et al., 2012; Worbe, Savulich, de Wit, Fernandez-Egea, & Robbins, 2015). Pictures of fruit were replaced with non-food stimuli (e.g. cartoon animals) to avoid the potential confound of food stimuli in those with AN. The task involves 3 stages: instrumental discrimination training, instructed outcome devaluation, baseline Go/No Go test and Slips-of-Action test. Two versions of the task in which stimuli and outcome animal pictures were reversed, were counterbalanced across participants.

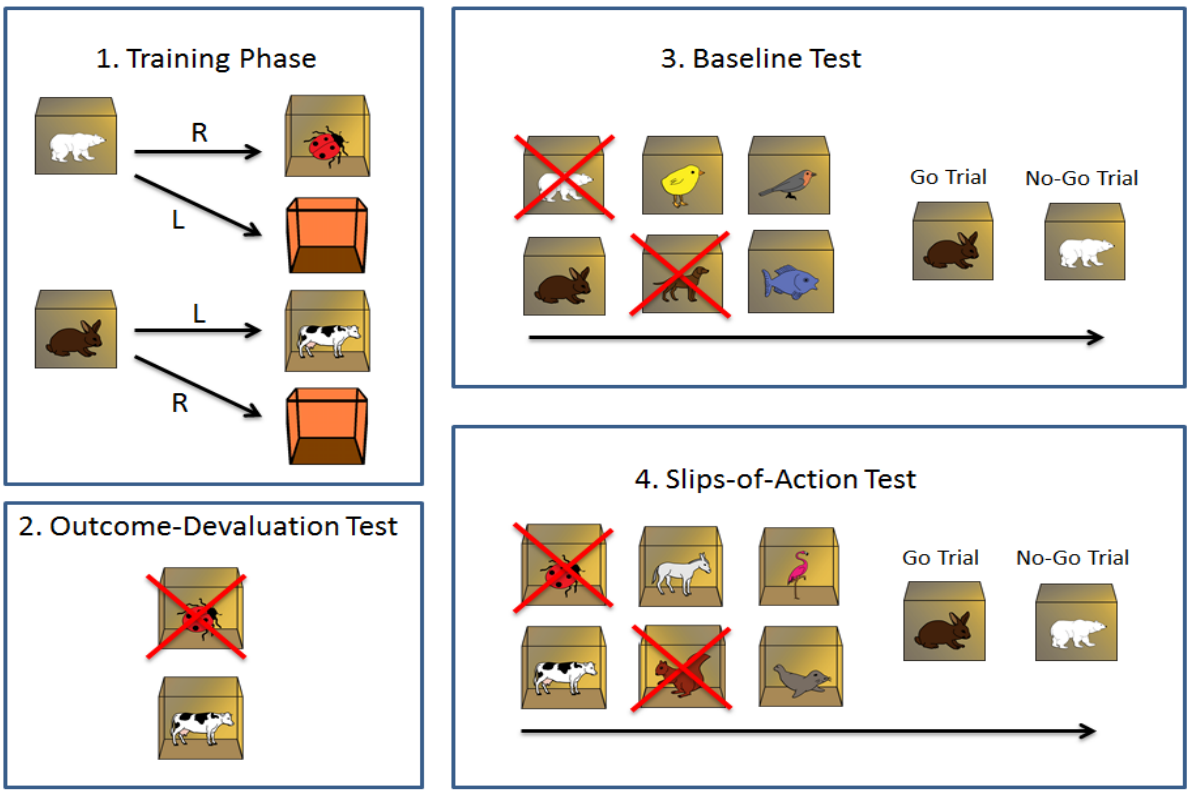
Instrumental discrimination training. On a computer screen, participants were presented with closed boxes that had pictures of animals superimposed on them. Their task was to learn by trial and error which key (the left "z" or the right "m") opened each box to reveal another animal prize inside, which added points to their total (See Figure 4.2, Training Phase). For example, in Figure 4.2 the polar bear signals that pressing right will lead to the ladybird, which will result in gaining points. Performance during this learning stage could be supported by both the goal-directed system (Stimulus-Outcome-Response; e.g., polar bear-ladybird-right) or by the habitual system (Stimulus-Response; e.g., polar bear-right). The faster the correct response, the more points were earned. Participants were awarded 5 points for correct responses within 0–1 second; 4 points for 1–1.5 seconds; 3 points for 1.5–2 seconds; 2 points for 2–2.5 seconds; and 1 point for >2.5 seconds. The stage was divided in 8 blocks of 12 trials each (96 trials in total). There were six stimuli-outcome associations to learn.

Instructed outcome devaluation test. In the instructed outcome devaluation test, participants were presented with two open boxes on the screen with two different animals inside; one animal was previously earned by pressing the left-hand key and the other by pressing the right-hand key. One of the animals was shown with a cross (an X) superimposed on it to indicate that it was no longer worth any points (it was devalued) (See Figure 4.2, Outcome-Devaluation Test). Participants were instructed to press the corresponding key that had previously opened the box to the still-valuable animal, and gained points. This stage consisted of 36 trials in one block. No performance feedback was provided to participants during this stage.

Slips-of-action test and baseline test. In the slips-of-action test, each of the test blocks (6 blocks in total) started with a 10-second screen showing the six different animal outcomes (inside open boxes) from the initial training stage. Two of these animal icons were marked with a cross indicating that opening the box that contained these animals would result in subtraction of points. Following this screen, a series of closed boxes marked with animal stimuli from the training phase were presented in quick succession (2 seconds per trial). Participants could earn points by pressing the appropriate keys to open the boxes with still-valuable animal outcomes inside. However, whenever they were presented with a stimulus for which the outcome inside is devalued, they could avoid losing points by refraining from pressing either key (See Figure 4.2, Slips-of-Action test). Each of the six stimuli were shown four times in each block (144 trials in total), and each outcome was devalued twice across blocks. Goal-directed action control was thus reflected in selective responses to valuable as opposed to devalued outcomes. In contrast, if the habitual system exerts dominant control over behaviour, this results in slips of action toward devalued outcomes. Each closed box was shown for 1 second and then replaced by another box with a different stimulus after a 1-second inter-trial interval.

An additional baseline Go/No-Go test was also used; in which participants were instructed to withhold their response for a subset of the stimuli ("No-Go trials") while still responding to the other stimuli ("Go trials"). This test is identical to the slips-of-action test, except that participants were initially shown the 6 *closed boxes* with fruit stimuli on the *outside* at the beginning of each test block. Two of these animal icons were again marked with a cross indicating that opening a box that contained these animals would result in a subtraction of points. Following this screen, a series of closed boxes marked with animal stimuli from the training phase were presented in quick succession. Participants could earn points by pressing the appropriate keys to open the boxes with valuable animals on the *outside*. However, whenever they were presented with a stimulus for which the animal on the outside was devalued, they could avoid losing points by refraining from pressing either key (See Figure 4.2, Baseline Test). This baseline test was included to control for general task demands, such as inhibitory control and working memory (de Wit et al., 2012; Geurts & de Wit, 2014). The order of the slips-of-action and baseline test was counterbalanced across participants

Figure 4.2 The four stages of the Slips-of-Action Paradigm



Questionnaires of contingency knowledge: After the behavioural experiment, participants were asked to complete questionnaires assessing their knowledge of the stimulus-response-outcome contingencies learned during the instrumental training stage. They were also asked to rate their confidence in their answers on a 1 to 100 scale.

4.5.5. Data Analysis

Data from both tasks were statistically analysed using repeated measures analysis of variance, and Spearman's rho in SPSS. One AN-C participant was not included in analysis of the Noise Avoidance Paradigm due to non-compliance with the task procedure. In the analysis of the Slips-of-Action Paradigm, 1 HC participant was not included due to failure of equipment, and one AN-R participant was not included due to non-compliance with the task procedure. VAS scales of mood, appetite, and ED related variables were compared across groups prior to each task using a series of one-way ANOVAs. To identify any differences in VAS measures of mood, appetite or ED variables across tasks, repeated measures ANOVAs were used.

In addition to the above analyses, a bayesian statistical analysis was performed on the data from both tasks. Bayesian ANOVAs were performed on responses to devalued stimuli and the difference scores (valued-devalued responses) for each tasks. An advantage of bayesian analysis is that it allows a comparative approach to assess the probability of the null and alternative hypotheses given the observed data, whereas frequentist methods only provide information regarding the null hypothesis (Jarosz & Wiley, 2014). Bayes Factor (BF_{01}) values provide an indicator of how many times more likely the null hypothesis is to the alternative hypothesis (Jarosz & Wiley, 2014). For example, a BF_{01} of 3-10 is considered substantial evidence for the null hypothesis, and suggests this is 3-10 times more likely that the alternative. A value of above 10 would be considered strong evidence in favour of the null hypothesis, whereas a value below 3 would provide only weak evidence that the null hypothesis is more likely than the alternative (Jeffreys, 1961). The analysis was carried out in JASP (Love et al., 2015). The program's default option of a Cauchy prior was used, and defined the width as .707.

4.6 Results

4.6.1 Demographics

Table 4.1 summarises the demographic and psychological characteristics of the three experimental groups.

Table 4.1. Demographics and psychological characteristics.

	AN-C (n=13)		AN-R (n=14)		HC (n=17)		Significance (p two tailed)	Post hoc group comparisons (p<.05)
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Age	31.15	7.96	27.07	6.49	24.06	5.60	.011	AN-C>HC
BMI	15.79	1.91	20.94	1.63	21.24	1.90	<.001	HC, AN-R>AN-C
Lowest BMI	13.02	1.15	13.8	1.23	---	---	.104	---
Age of Onset	20.33	5.74	16.5	2.1	---	---	.028	AN-C>AN-R
Duration of AN	10.25	5.2	5.75	4.15	---	---	.022	AN-C>AN-R
NART	113.84	7.54	114.57	6.77	109.29	7.43	.100	---
Years in Education	18.17	4.26	18.64	2.66	16.81	2.23	.286	---
EDE	3.10	1.44	0.74	0.61	0.22	0.20	<.001	AN-C>AN-R, HC
EDE-Q	3.36	1.74	0.95	0.85	0.46	0.32	<.001	AN-C>AN-R, HC
AAQ	32.54	12.64	48.0	9.20	56.82	8.29	<.001	AN-C<AN-R, HC
SPSRQ Punishment	15.46	5.91	12.07	4.70	8.53	3.84	.001	An-C>HC
SPSRQ Reward	8.08	4.29	8.86	4.28	9.06	3.54	.791	---
BIS	56.46	12.53	61.57	9.72	54.94	11.74	.264	---

	AN-C (n=13)		AN-R (n=14)		HC (n=17)		Significance (p two tailed)	Post hoc group comparisons (p<.05)
CIA	29.46	12.43	7.93	6.5	1.76	2.25	<.001	AN-C>AN-R, HC
OCI-r	20.85	15.78	10.79	6.45	6.06	6.94	.006	AN-C> HC
BDI	29.62	18.12	6.36	6.43	3.06	4.41	<.001	AN-C>AN-R, HC
STAI-State	50.08	13.04	34.43	5.45	26.53	6.56	<.001	AN-C>AN-R> HC
STAI-Trait	60.69	12.91	45.21	10.56	32.59	9.51	<.001	AN-C>AN-R> HC
YBC-EDs Current	16.38	8.21	3.79	3.95	0	0	<.001	AN-C>AN-R, HC
YBC-EDs Past	24.62	5.30	23.82	5.30	0	0	<.001	AN-C, AN-R> HC
SS	53.08	30.03	5.29	8.36	0.24	0.75	<.001	AN-C>AN-R, HC

Note: BMI = Body Mass Index; NART = National Adult Reading Test; EDE= Eating Disorder Examination; EDE-Q = Eating Disorder Examination Questionnaire; AAQ = Acceptance and Action Questionnaire; SPSRQ = Sensitivity to Punishment and Sensitivity to Reward Questionnaire; BIS = Barratt Impulsiveness Questionnaire; CIA = Clinical Impairment Assesment; OCI-r = Obsesssive Compulsive Inventory Revised; BDI = Beck Depression Inventory; STAI = State Trait Anxiety Inventory ; YBC-EDS-SRQ = Yale-Brown-Cornell Eating Disorder Scale Self-Report Questionnaire; SS = Self-Starvation Scale.

-- No signifcant differences

4.6.2 VAS Scales

A series of one-way ANOVAs were used to examine differences in VAS scales of mood, appetite and ED-related variables across groups for each task session. Prior to the Noise Avoidance Paradigm, there were significant group differences in ratings of happiness ($F[2,42]=3.855$, $p=.029$), hunger ($F[2,42]=5.273$, $p=.009$), desire to eat ($F[2,42]=7.655$, $p=.002$), and fear of fatness ($F[2,42]=15.86$, $p<.001$). Bonferroni corrected post-hoc analyses indicated significantly higher happiness, hunger, and desire to eat in the HC compared to AN-C group ($p<.05$). Fear of fatness followed a pattern of AN-C> AN-R>HC ($p<.05$).

Prior to the Slips-of-Action Paradigm, there were significant group differences in ratings of happiness ($F[2,42]=3.816$, $p=.030$), anxiety ($F[2,42]=11.45$, $p<.001$), hunger ($F[2,42]=7.37$, $p=.002$), fullness ($F[2,42]=4.033$, $p=.025$), desire to eat ($F[2,42]=8.874$, $p=.001$), and fear of fatness ($F[2,42]=14.86$, $p=<.001$). Bonferroni corrected post-hoc analyses indicated significantly higher happiness, fullness, and desire to eat in the HC compared to AN-C group ($p<.05$).The HC group reported significantly higher levels of hunger than both the AN-C and AN-R groups ($p<.05$). Anxiety was higher in the AN-C compared to both the HC and AN-R group ($p<.05$). Fear of fatness followed a pattern of AN-C> AN-R>HC ($p<.05$).

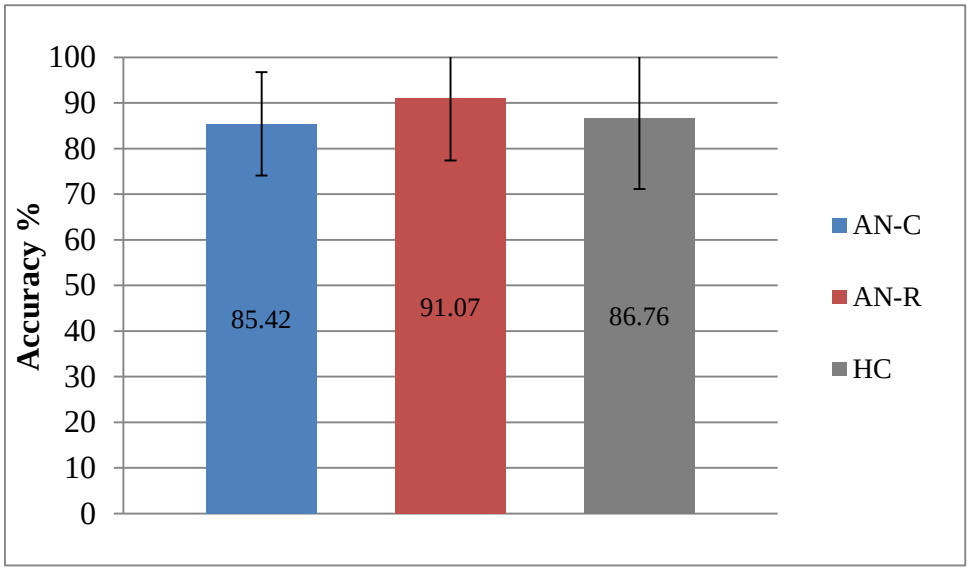
To examine any differences in VAS scales of mood, appetite and ED-related variables across task sessions, a series of repeated measures ANOVAs were conducted. For all three groups, there were no significant main effects of task session ($p>.05$), or task session*rating interaction ($p>.05$), suggesting there were no significant differences in any of the ratings across task sessions. The means and standard deviations for VAS scales across task sessions are shown in Appendix 4.11.

4.6.2 Noise Avoidance Paradigm

4.7.2.1 Training Stage

There was no significant difference between groups in accuracy during the initial training stage of the task, F(2,40)=.611, p=.548 (See Figure 4. 3), or in overall reaction times, F(2,40) =1.059, p=.356, suggesting all three groups were equally proficient in learning the task contingencies.

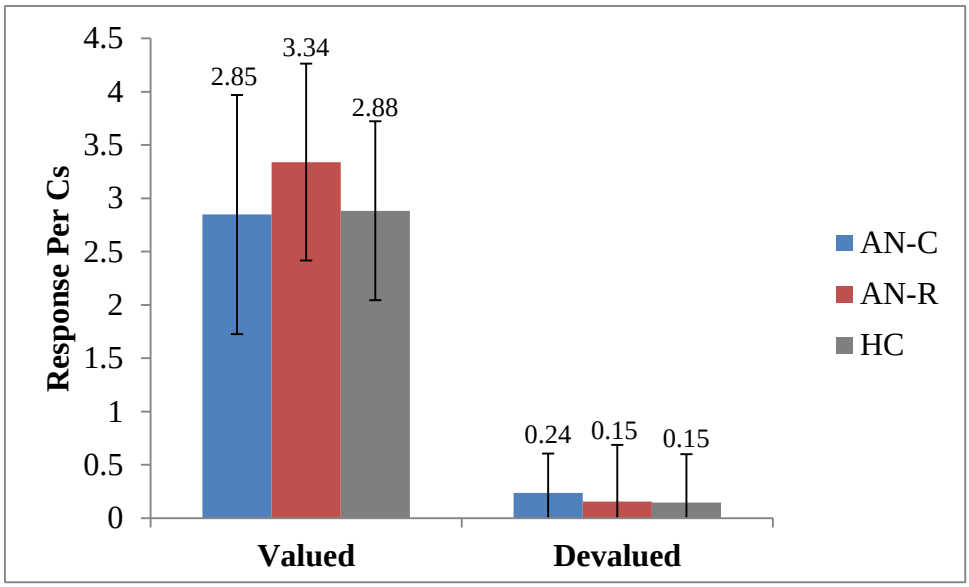
Figure 4.3 Accuracy (%) during training across groups



4.6.2.2 Devaluation Sensitivity Test

Prior to the extended training phase, a main effect of devaluation was observed F(1,40)=291.217, p<.001, suggesting all groups responded more to the valued stimulus than the devalued stimulus. There was no main effect of group, F(2,40)=.881, p=.422, or group*devaluation interaction, F(2,40)=1.058, P=.357, suggesting all groups were equally able to withhold unnecessary responses to the stimulus with a devalued outcome (see Figure 4.4).

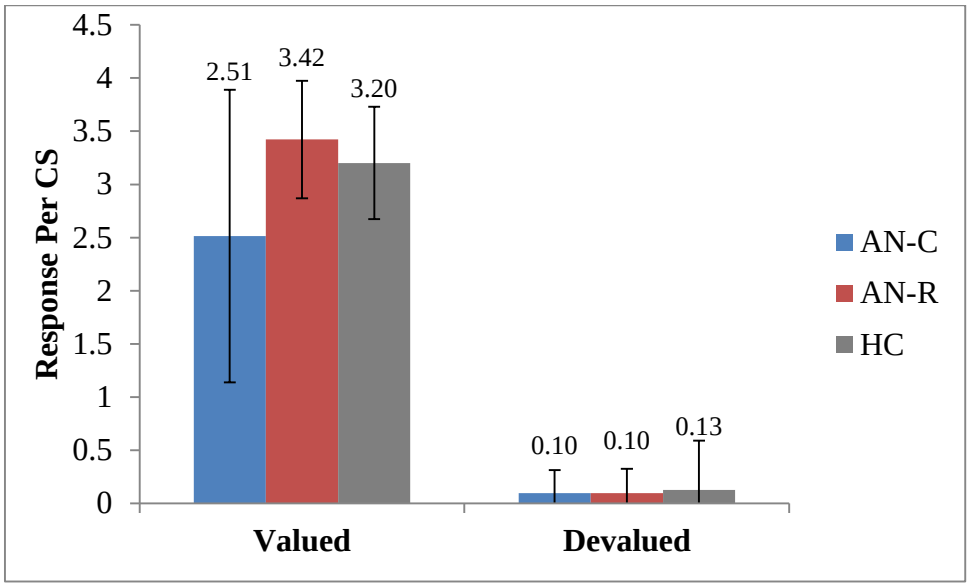
Figure 4.4 Responses to valued and devalued stimuli during the devaluation sensitivity test



4.6.2.3 Habit Test

Following the extended training phase, a strong devaluation effect was seen across groups, $F(1,40)=404.414$, $p=<.001$, indicating all three groups again responded more to the valued stimulus than the devalued stimulus (see Figure 4.5). There was a significant overall effect of group, $F(2,40)=3.686$, $p=.034$, and a near significant group*devaluation interaction, $F(2,40)=3.135$, $p=.054$. Post-hoc comparisons revealed this was driven by a significant group difference in responses to valued stimulus, $F(2,40)=3.923$, $p=.028$. Bonferonni corrected pairwise comparisons indicated increased responding to the valued stimuli in the AN-R (mean: 3.42) compared to the AN-C (mean: 2.51) group ($p<.05$). There were no significant differences in responses to the devalued stimuli between groups, $F(2,40)=.044$, $p=.957$.

Figure 4.5 Responses to valued and devalued stimuli following overtraining



Controlling for age and depression

There was a significant difference in age between the AN-C and HC groups. For this reason the analysis of the habit test was repeated with age added as a covariate. As a number of participants met the criteria for current or past depression, this was also added into the analysis as a covariate. The pattern of results remained the same when controlling for the variance associated with age and depression. There was still a main effect of devaluation, $F(1,389)= 68.93$, $p<.001$, and no devaluation*group interaction was seen, $p>.05$.

Comparing medicated and un-medicated participants

As some of the participants in the AN-C and AN-R group were taking antidepressant or antipsychotic medications, responses to valued and devalued stimuli in the habit test were compared across medicated and un-medicated participants. When comparing these groups, there was again a main effect of devaluation, $F(1,241)=176.33$, $p<.001$, and no devaluation*group interaction, $F(1,24) = 1.337$, $p=.259$. This suggests medicated and un-

medicated participants did not differ in their responses to valued and devalued stimuli following the extended training phase.

4.6.2.4 Questionnaire Data

All participants correctly recalled the two stimulus-response, and response-outcome contingencies learned during the task. There was no significant difference between groups in expectation of noise (following devaluation), $F(2,40)=.635$, $p=.535$, urge to respond to devalued stimuli, $F(2,40)=.935$, $p=.401$, or suppression of response to devalued stimuli, $F(2,40)=.025$, $p=.976$ (means and standard deviations for expectation, urge to respond and suppression of response are given in Table 4.2).

Table 4.2 Questionnaire ratings for expectation, urge to respond and suppression of response.

	Expectation		**Urge to respond**		**Suppression of response**	
Group	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
AN-C	23.92	31.41	47.33	31.89	38.0	24.48
AN-R	12.64	20.6	31.07	28.1	35.57	28.23
HC	19.47	25.43	37.65	30.92	37.12	30.99

4.6.2.5 Correlations with clinical measures

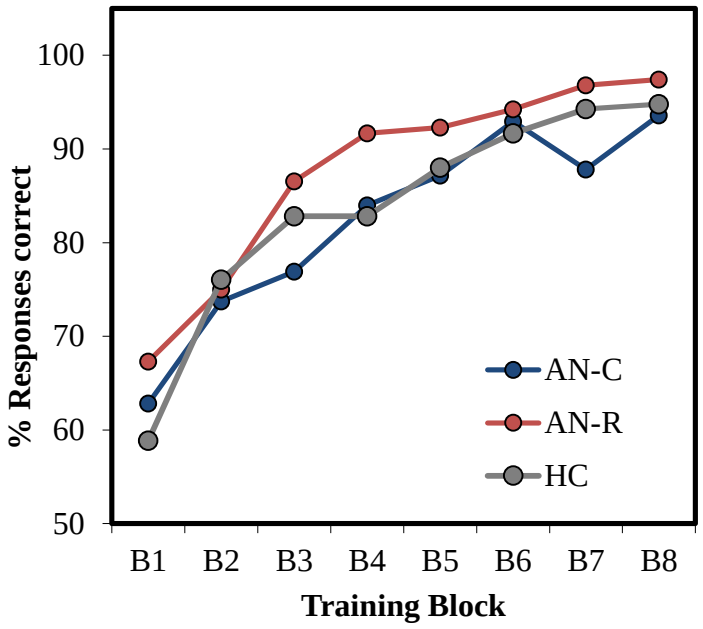
No correlations between the questionnaire measures and performance on the habit test survived bonferroni correction for multiple comparisons.

4.6.3. The Slips-of-Action Paradigm

4.6.3.1 Instrumental Discrimination Training

There was no difference between groups in rate of learning in the instrumental discrimination training stage in terms of accuracy, F(8.3, 166.1)=0.834, p=.577, (see Figure 4.6), or reaction times, F(6.6, 131.6)=1.171, p=.325. This suggests all groups were equally able to learn the contingencies during this training stage.

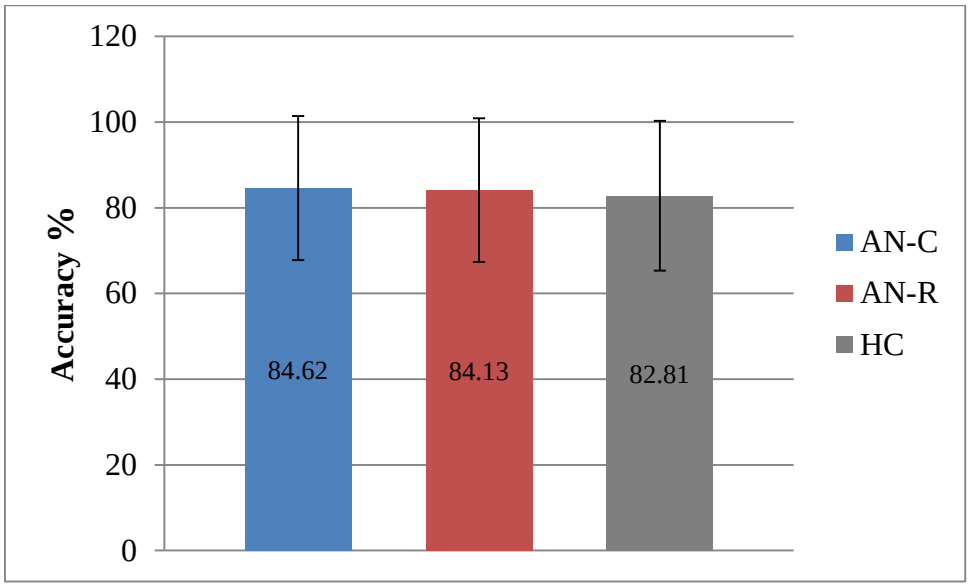
Figure 4.6. Response accuracy over the course of six blocks in the Instrumental Discrimination Training stage across groups.



4.6.3.2 Instructed outcome devaluation test

There was no significant difference between groups in accuracy during the instructed outcome devaluation test, F(2,40)=.044, p=.957 or in RTs, F(2, 40) =2.323. p=.111. This illustrates that the groups were equally capable of directing their responses towards still-valuable outcomes.

Figure 4.7. Mean group accuracy (%) in the Outcome Devaluation Test

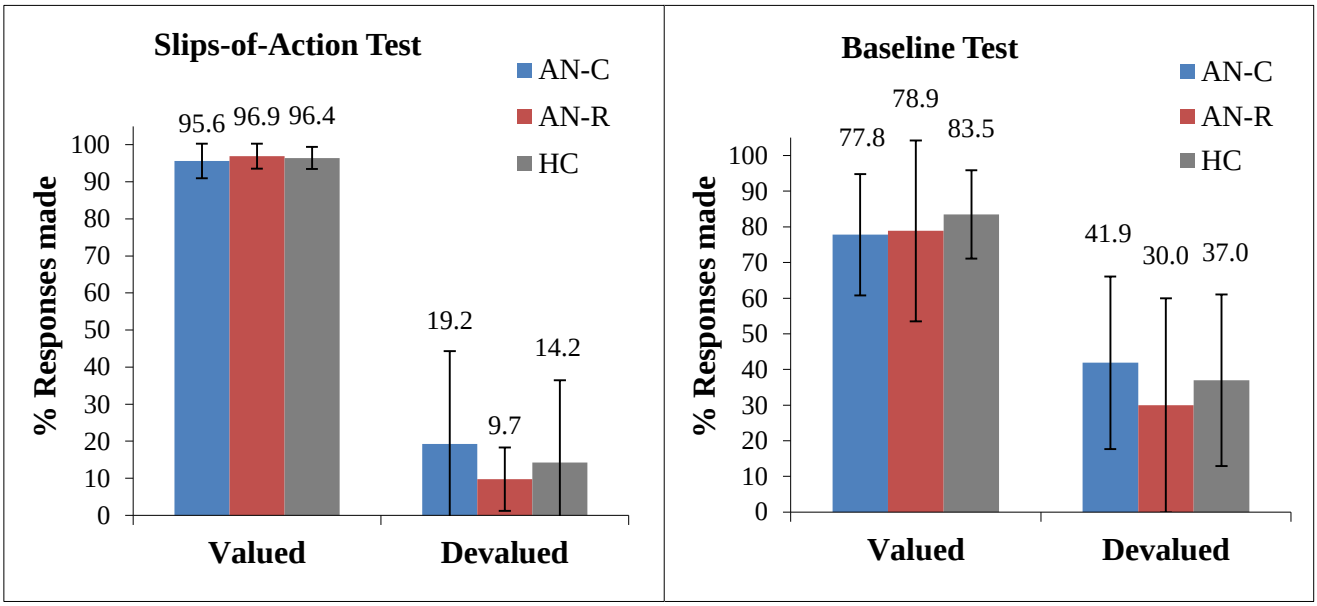


4.6.3.3. Slips-of-Action and Baseline Go/No Go Test

The two tasks were combined for a repeated measured ANOVA, with a within-subjects factors of test type (slips-of-action versus baseline test), and devaluation (valued versus devalued), and a between-subjects factor of group (AN-C, AN-R and HC). This analysis yielded a significant main effect of devaluation, $F(2,40) = 291.822$, $p<.001$, indicating all participants were able to withhold responses associated with devalued events, and continue to respond to valuable stimuli in the slips-of-action and baseline tests. A significant devaluation*task interaction, $F(1,40) = 45.268$, $p<.001$, suggesting that this was more challenging during the slips-of-action compared to the baseline task. This was confirmed by separate follow-up analyses: on the slips-of-action test more devalued responses were made than on the baseline test, $F(1,40) = 26.865$, $p<.001$, and less valuable responses, $F(1,40) = 35.07$, $p<.001$. This is unsurprising, as the slips-of-action should be more challenging, considering that responding needs to be based on the evaluation of the anticipated outcome.

There was no significant group*devaluation*task interaction (F[2,40]=.061, p=.941), or group*devaluation interaction found (F[2,40]=.831,p=.443). This indicates there were no group differences in the ability to withhold previously rewarded responses when the outcome is devalued (see Figure 4.8), and suggests individuals with experience of AN are not impaired in this ability compared to controls.

Figure 4.8 Responses for valuable versus devalued outcomes during the slips-of action test (left panel); responses for valuable versus devalued stimuli during the baseline test (right panel).



Controlling for age and depression

Age and depression were again added as covariates in the analysis of the slips-of-action and baseline tests. The pattern of results remained the same when controlling for the variance associated with age and depression, with no group*devaluation*test interaction, or group*devaluation interaction, Fs<1.

Comparing medicated and un-medicated participants

Responses to valued and devalued outcomes in the slips-of-action test in medicated and un-medicated participants in this group were again compared. When comparing these groups, there was a main effect devaluation, $F(1,25)=28.98$, $p=<.001$, but no devaluation*group interaction, $F(1,25) = .529$, $p=.474$. This suggests medicated and un-medicated participants in the AN groups again did not differ in their responses to valued and devalued stimuli in the slips-of-action test.

4.6.3.5. Questionnaire Data

There was no significant difference between groups in explicit knowledge of stimulus-response, $F(2,40)=.948$, $p=.396$, response-outcome $F(2,40)=.190$, $p=.828$, or stimulus-outcome contingencies $F(2,40)=.618$, $p=.544$. There were also no differences in self-reported confidence regarding the different contingencies: stimulus-response, $F(2,40)= 1.295$, $p=.285$, response-outcome, $F(2,40) = .487$, $p=.618$, stimulus-outcome, $F(2,40) = .760$, $p=.474$. Means and standard deviations for explicit contingency knowledge and confidence ratings are shown in Table 4.3.

Table 4.3 Explicit knowledge scores (out of 6) and confidence ratings (out of 100) across groups

	AN-C Group		AN-R Group		HC Group	
Contingency	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Stimulus-Response	5.46	0.29	5.79	0.15	5.81	0.14
Confidence Rating	72.1	7.12	77.2	4.07	83.1	3.40
Response-Outcome	4.85	0.42	5.14	0.38	4.88	0.33
Confidence Rating	58.6	7.83	59.8	6.13	66.7	5.35
Stimulus-Outcome	4.54	0.60	5.00	0.47	4.19	0.52
Confidence Rating	51.8	9.36	53.0	6.83	63.3	6.15

4.6.3.6. Correlations with clinical measures

No correlations between questionnaire measures and performance on the habit task (valued stimulus responses minus devalued stimulus responses) survived bonferroni correction for multiple comparisons.

4.6.4 Bayesian Analyses

Bayes Factor (BF_{01}) values for both tasks are provided in Table 4.4. With the exception of the difference scores in the Noise Avoidance Paradigm, the BF_{01} values suggest substantial evidence in favour of the null hypothesis (Jeffreys, 1961), suggesting there are no differences between groups in performance on the tasks. The BF_{01} value for the difference scores in the Noise Avoidance Paradigm suggests only anecdotal evidence for the null hypothesis (Jeffreys, 1961), which is likely due to the increased response in the AN-R group to the still valuable stimuli reported above. All other values suggest the null hypothesis is between 3.6 and 5.7 times more likely than the alternative hypothesis.

Table 4.4. BF_{01} values for the Devalued and Difference scores across tasks

Task	Devalued	Difference
Noise Avoidance Paradigm	5.674	0.742
Slips of Action Paradigm	3.630	4.284

4.7 Summary of Results

- Participants in all three groups were equally successful at using feedback to learn the stimulus-response contingencies during both tasks.
- Participants in all three groups responded less to the devalued compared to valued stimuli following extended training on both tasks, suggesting individuals with experience of AN (current and past) did not show a tendency towards responding habitually in either task.
- A tendency towards habits was not observed when controlling for differences in age and levels of depression, and no differences were found when comparing medicated and unmediated individuals in the AN groups.
- Participants in all three groups had intact explicit knowledge of stimulus-response-outcome contingencies in both tasks.
- Bayesian analyses further supports the null hypothesis suggesting there are no differences in performance between groups.

4.8 Discussion

In this study, no evidence was found for a bias towards developing habits in participants with current or past AN using two validated outcome devaluation tasks assessing both appetitive and avoidance habits. All participants were equally successful at using feedback to learn the correct stimulus-response contingencies in the initial training phase of both tasks, and explicit knowledge of contingencies was equal across groups. Following devaluation of outcomes, participants with current and past AN were equally able to withhold responses to devalued stimuli in comparison to healthy control participants in both tasks, suggesting intact goal-directed learning. This result was further supported by a Bayesian analysis, which suggested the null hypothesis (i.e. there is no difference in response to devalued stimuli between groups) was 3.6-5.7 times more likely than the alternative hypothesis (i.e. there is a between-group difference in response to devalued stimuli).

4.8.1 Does Anorexia Nervosa involve a generalised tendency towards habits in learning?

The results of this study suggest that AN may not involve a pervasive vulnerability to developing stimulus-response habits in instrumental learning, which is in conflict with the hypotheses of this chapter. These findings in AN differ from studies involving individuals with OCD and addictive disorders, in which excessive habitual responding has been found using these tasks (Gillan et al., 2015; Gillan et al., 2013; Gillan et al., 2011; Sjoerds et al., 2013). This is surprising considering suggestions of both behavioural and neurobiological parallels between AN and these disorders.

Whilst null results should be interpreted with caution, the results of a bayesian analysis further support the conclusion that those with current and past AN do not show a

generalised tendency towards habits in the tasks used in this study. However, limitations of the outcome-devaluation tasks used in this study should be noted. The tasks used may not have been sensitive enough to pick up a potentially subtle deficit in goal-directed control of behaviour. Both tasks involved training on a limited number of simple contingencies, which are used for the entirety of the task. Additionally, the motivational value of correctly responding to these stimuli (i.e. to gain points or avoid an aversive noise) may not be particularly salient or important to individuals. As such these tasks have low ecological validity, and may not pick up a tendency to rely on habits in real-life situations, which involve more complex decision making and reward processing. Future research may benefit from the use of alternative experimental tasks used to assess deficits in goal-directed control of behaviour, such as those that require participants to track changing contingencies and outcomes on a trial-by-trial basis (Voon et al., 2014). The task used by Voon et al (2014) allows the assessment of the contribution of different learning mechanisms in acquiring behaviour. Participants were asked to make two-step sequential decisions between pairs of stimuli on a trial-by-trial basis, with a varying probability that the each stimulus in choice one will lead to a certain stimuli pair in choice two. The stimuli in choice two also vary in their probability of gaining a reward if chosen. The decisions made are expected to differ depending on the contribution of two types of learning; model-free and model-based. Model-free learning uses the experience of previous trials to determine the decision, which reinforces previous actions, giving rise to habitual behaviour. Model-based learning tracks the changing probabilities of reward to produce goal-directed decisions. Successful performance on this task requires participant to track the changing value and probability of reward in order to perform in a goal-directed manner, a process which is much closer to that involved in the acquisition of behaviour in real-life situations (Voon et al., 2014). Using this task in individuals with AN may enable

the detection of more subtle deficits in the balance between goal-directed and habitual control of behaviour.

It is also possible that the relevant aspect of dysfunctional habit learning in AN is not being measured by the tasks used in this study. One aspect of successful goal-directed learning is the ability to flexibly update the value of the outcome of an action based on the individual's current internal state (e.g. a state of hunger which increases the value of food) (Griffiths, Morris, & Balleine, 2014). The tasks used in this study explicitly instructed participants that certain stimuli were no longer valuable and should no longer be responded to; therefore they were not required to assess value in a self-referential way. It may be that compulsive weight-loss habits in AN develop from an inability to update the value of an outcome based on the individuals internal state. AN has often been associated with low interoceptive awareness (Kaye et al., 2009), which is characterised by an inability to recognise emotional states and discriminating bodily sensations such as hunger and satiety (Fassino et al., 2004). Individuals with AN show altered subjective responses to a number of interoceptive stimuli such as food, hunger/satiety and pain (de Zwaan, Biener, Bach, Wiesnagrotzki, & Stacher, 1996; Lautenbacher, Pauls, Strian, Pirke, & Krieg, 1990; Nakai & Koh, 2001; Santel, Baving, Krauel, Munte, & Rotte, 2006; Wagner et al., 2008). Altered activity in the amygdala in AN (Strigo et al., 2013; Wagner et al., 2008), an area suggested to be crucially involved in interoception (Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004), further supports these behavioural findings of aberrant interoceptive awareness in AN. If individuals with AN are unable to flexibly update the value of carrying out disorder-related behaviours on the basis of their current internal state, this may explain the persistence of this behaviour, which continues despite the negative physical and psychological consequences associated with this behaviour. If this is the case, this deficit

would not be picked up by the current tasks, in which the individual's current internal state is not relevant to updating the value of an outcome.

4.8.2. Are habits disorder-specific in Anorexia Nervosa?

Another possible interpretation of these findings is that habits in AN are disorder-specific, and as such are not picked up by the tasks used in this study. The neural aberrancies reported in AN have been suggested to reflect deficits in the neural circuitry associated with goal-directed and habitual control of behaviour (Rothemund et al., 2011; Steinglass et al., 2015), but this is not supported by the results of this study. However, functional imaging studies in AN often use symptom provocation paradigms, and as such overlapping neural circuitry may be reflective of disorder-specific responses in AN.

Individuals with AN experience intense reward from the pursuit of thinness (Park et al., 2014), reflected by increased salience and neural response to disorder-related stimuli in reward and habit-related regions in AN (Cowdrey et al., 2011; Fladung et al., 2010; Fladung et al., 2013; Giel et al., 2013; Steinglass et al., 2015). Food restriction is also linked to an upregulation of reward (Fulton et al., 2004), and as such may increase the rewarding value of weight-loss behaviour in individuals with AN. The rewarding value held by weight-loss behaviour in AN may lead to repetition of this behaviour in pursuit of reward, a prerequisite for the development of habits. In addition, the evidence reviewed in Section 1.11 suggests that the physiological consequences of starvation promote compulsivity and habit learning, and increase reward sensitivity. The combination of an increased drive to pursue the rewarding effects of weight-loss, and the enhancement of habits during starvation may create conditions which drive the development of weight-loss habits in AN. Thus, whilst this study suggests that AN may not involve a generalised

vulnerability to forming habits, disorder-specific habits may develop in the context of aberrant reward and starvation.

The development of disorder-specific habits in AN is partially supported by a recent study investigating food-based reversal learning in recent onset restrictive AN (Hildebrandt et al., 2015). In this study, Hildebrandt et al (2015) used a reversal learning paradigm in which an unconditioned visual food stimulus (M&Ms) was paired with one of two neutral stimuli. Subsequently this association was reversed, with food being paired with the alternate stimulus. To increase saliency, individuals were informed that they would receive the actual food stimulus once the experiment was over. Individuals with AN showed clear deficits in their ability to extinguish food-cue responses during the reversal phase, and a disgust response from the facial muscles was predictive of this difficulty. This is in contrast to a previous study of reversal learning in AN, using disorder-neutral stimuli, in which only subtle deficits were reported (Sarrar et al., 2011). The authors suggest that disgust-conditioning may underpin food avoidance in a way that may facilitate habits in AN, with the initial reinforcing effects of reducing the aversive emotions associated with food supporting a transition to habits over time (Hildebrandt et al., 2015).

4.8.3 Increased responding to valuable stimuli in individuals recovered from Anorexia Nervosa

An unanticipated finding was the significantly increased responding to valued stimuli following extended training in the recovered AN group compared to the current AN group in the Noise Avoidance Paradigm, suggesting increased accuracy of response in this group. There may several possible explanations for this. Studies have shown that whilst performance on tasks tapping executive functions, such as cognitive flexibility, are often decreased in acute AN, this may normalise to some extent after recovery (Carina

Gillberg, Råstam, Wentz, & Gillberg, 2007; Holliday et al., 2005). Thus, a decreased response to valuable stimuli may reflect the decreased ability to perform the task efficiently in the acute AN groups, due to neuropsychological deficits, which are no longer seen after recovery. However, this does not explain the lack of a significant difference between the AN and the HC group, the latter whom also appear to have slightly decreased responses to valuable stimuli compared to the recovered group.

Of relevance to this result may be the significant difference between age of onset and duration of illness between the current and recovered AN groups in this study. The recovered group reported a significantly younger age of onset (16.5 vs 20.3) and a significantly shorter duration of illness (5.75 vs 10.25). A previous study investigating set-shifting ability, a measure of cognitive flexibility, found *improved* performance in adolescent AN compared to healthy controls, indicated by higher accuracy across all trials and a reduced error rate (Bühren et al., 2012). The authors suggest this absence of a deficit in set-shifting may be due to a shorter duration of illness, and younger age in the adolescent sample. They link the increased accuracy in this sample to the high levels of perfectionism reported in adolescent AN, which are also reflected in response reaction times, suggesting participants may have taken longer to ensure greater accuracy (Bühren et al., 2012). The differences in age of onset and duration of illness across the AN groups in this study may thus help explain the increased accuracy of the recovered AN group in the Noise Avoidance Paradigm. The shorter duration and earlier age of onset in the recovered AN group may be linked to less cognitive impairment in these individuals, compared to the longer duration and later onset in the current AN group. This may also help to explain the observed higher accuracy in the recovered group compared to the HC group, in which a perfectionistic style combined with less cognitive impairment may have led to increased accuracy. This increased response to valuable stimuli in the recovered group likely

underpins the inconclusive results of the Bayesian analysis of the difference scores in the Noise Avoidance Paradigm, which suggested only weak evidence in favour of the null hypothesis (i.e. no group differences).

4.8.4 Limitations

In addition to the limitations of the outcome devaluation tasks discussed in Section 4.8.1, there are other limitations of note. The sample size was relatively small, potentially limiting the power to detect differences in the tasks used. However, the addition of a bayesian analysis providing further evidence in favour of the null hypothesis, adds weight to the robustness of our observation that individuals with AN do not display an aberrancy in habit formation in the context of these established outcome-devaluation tasks. Whilst the results do not indicate any sort of trend towards habitual control of behaviour in either task, replication with larger samples is needed. In addition the sample was limited to those who had never exhibited significant binge/purge symptoms. Due to the small nature of the study, it was decided that it was necessary to isolate a sample who displayed only the extreme control associated with relentless and habitual self-starvation in AN. The cycle of binge/purge behaviour may also be considered to have an element of compulsivity (Gearhardt et al., 2009; Gearhardt, White, et al., 2011), and future studies may benefit from the inclusion of those with binge/purge symptoms and comparison between subtypes. However, in an unpublished study carried out in parallel to the current study, no evidence was found for habits using the original slips-of-action paradigm in either subtype of AN (Godier et al., under review).

There was also a significant difference in age between the AN-C and HC groups. Age-related differences in the balance between goal directed and habitual control of behaviour have been shown using one of the tasks implemented in this study, and

suggested a shift to a reliance on habits in healthy ageing (de Wit, van de Vijver, & Ridderinkhof, 2014). However, as the AN-C group were significantly *older* than the HC group, this should enhance any impairment in goal-directed behaviour in this group, and as such is an unlikely explanation of the absence of group differences in habitual responding. Including age as a covariate in the analysis of both tasks did not reveal any group differences, suggesting age-related differences in habitual responding were not masking a group effect.

A number of participants in the AN groups were taking serotonergic antidepressants (SSRI's and SNRI's), and a few were also taking antipsychotics. Animal research has shown decreased sensitivity to outcome devaluation as a result of serotonin receptor antagonism or serotonin depletion (Altman & Normile, 1986; Clarke, Walker, Dalley, Robbins, & Roberts, 2007). Furthermore, a recent study investigating tryptophan (a precursor to serotonin) depletion in humans found this promoted a reliance on habits in the slips-of-action task (Worbe et al., 2015), and so an effect of serotonergic medication cannot be ruled out. However, there was no significant difference in response to devalued stimuli between medicated and un-medicated participants in the AN groups, although this analysis is limited by the small size of these groups.

4.8.5 Conclusions

In sum, this is the first study to assess the balance between goal-directed and habitual control of behaviour in individuals with experience of AN, and provided no evidence of a reliance on either appetitive or avoidance habits in two established outcome devaluation tasks. Whilst the data from these tasks suggest AN does not involve a generalised reliance on habits in learning, it remains to be seen whether habit formation is engaged when it comes to disorder-specific behaviours. The development of tasks using disorder-relevant stimuli will be of importance in investigating this possibility. Before concluding that a generalised reliance on habits is not evident in AN, future investigation with alternative tasks, and replication in a larger sample and across AN subtypes is needed.

5. Resting State Neural Networks in Anorexia Nervosa: An investigation using Magnetoencephalography.

5.1 Overview

Chapters 2 and 3 discussed parallels at the level of self-report between the compulsive nature of behaviour seen in AN and substance dependence. However, this was not supported by behavioural data reported in Chapter 4, which suggested individuals with AN do not show a tendency to rely on habits in outcome-devaluation tasks as previously shown in OCD and substance addiction. This was surprising considering parallels in the dysfunction of neuropsychological indices of compulsivity across these disorders discussed in Chapter 1. In Chapter 4 it was proposed that whilst there may be no pervasive tendency to rely on habits in AN, compulsive weight-loss behaviour may be the result of increased pursuit of aberrant disorder-related reward, and an enhancement of habit formation during starvation. This may be reflected in alterations in neural systems supporting compulsive behaviour in AN. To investigate the neural mechanisms that may be driving behaviour in AN, this chapter will investigate neural networks at rest in AN, and how this might related to self-reported compulsivity by addressing the following research questions:

- Do individuals with AN show aberrancies in neural networks at rest, and are these trait-related, evidenced by a persistence of dysfunction into recovery?
- Are aberrancies in neural resting state networks in AN associated with measures of compulsivity?

5.2 Background

The possibility of shared underlying behavioural and neurobiological mechanisms underpinning compulsive behaviour across psychiatric disorders has been a main focus of this thesis. Chapter 2 highlighted qualitative parallels with SUDs in the way compulsive behaviour is experienced in AN, and the data presented in Chapter 3 supported this by using the criteria for substance dependence to develop a useful measure of the compulsive nature of weight-loss behaviour in AN. Both of these chapters support similarities between the compulsive nature of behaviour in AN and addiction at the level of self-reported symptoms and subjective experience. However, in Chapter 4 this did not translate into a common underlying reliance on the habitual system in directing behaviour in outcome-devaluation tasks, previously reported across compulsive disorders (Gillan et al., 2015; Gillan et al., 2013; Gillan et al., 2011; Sjoerds et al., 2013; Voon et al., 2014). This was surprising considering both the behavioural parallels AN has with these disorders, discussed in Chapter 1, and aberrancies reported in AN in the neural circuitry suggested to be involved in goal-directed and habitual control of behaviour (Rothemund et al., 2011). As proposed in Chapter 4, it is possible that whilst individuals with AN may not have a *generalised* vulnerability to developing habits in learning, weight-loss behaviours may still become habitual over time as they are repeatedly engaged in over time. The increased salience of disorder-related reward reported in behavioural (Aspen, Darcy, & Lock, 2013; Brooks, Prince, Stahl, Campbell, & Treasure, 2011) and neuroimaging studies of AN (Cowdrey et al., 2011; Fladung et al., 2010; Fladung et al., 2013; Giel et al., 2013) may lead to an increased drive to repeat behaviour associated with rewarding weight-loss, and once repeated enough this may result in a shift towards habitual control of this behaviour (Walsh, 2013).

The RDoC initiative suggests that frontal-striatal circuitry involving the striatum and medial regions of the PFC are involved in construct of 'habits'. The development of disorder-specific habits in AN may lead to the aberrancies in this neural circuitry, and initial support for this has been reported in AN (Rothemund et al., 2011). This chapter aims to further investigate aberrancies in neural circuitry in AN using magnetoencephalography (MEG) at rest, and how dysfunction of these networks may relate to the compulsive nature of behaviour, measured by the Self-Starvation Scale developed in Chapter 3.

5.2.1 Resting State Functional Connectivity

In recent years there has been increasing interest in studying the connectivity between brain regions at rest. The synchronicity of spatially separate brain regions is thought to form networks which are integral to information processing (Brookes, Woolrich, et al., 2011). The majority of research in this area has used fMRI: fMRI blood-oxygen-level-dependent (BOLD) signal is measured in individuals at rest, whilst performing no particular task. BOLD signals are then correlated in time, with correlation indicating connectivity between regions (Biswal, Yetkin, Haughton, & Hyde, 1995). Regions showing a strong temporal coherence are termed ‘‘resting state networks" (RSNs) and are thought to reflect intrinsic properties of functional brain organisation (van den Heuvel & Hulshoff Pol, 2010). Alterations in resting state functional connectivity (rsFC) have been implicated in a number of neurodegenerative and psychiatric disorders, such as Alzheimer's disease, schizophrenia, depression, autism, attention deficit hyperactivity disorder and drug addiction (Lu & Stein, 2014).

5.2.2. Resting State Network Dysfunction in Anorexia Nervosa

The last few years have seen a number of studies published investigating rsFC in AN, and many have focussed on aberrancies in networks involved in self-referential processing (or rumination) and cognitive control. In the first published study of rsFC using fMRI in individuals recovered from AN, increased rsFC was found in the Default Mode Network (DMN), with the precuneus and dorsolateral prefrontal cortex (dlPFC) (Cowdrey, Filippini, Park, Smith, & McCabe, 2012). The DMN encompasses brain regions including the cingulate cortex, the precuneus, and parts of the PFC. It is more active at rest than during attention-demanding tasks, and is therefore thought to be associated with stimulus-independent thought and self-reflection (Raichle et al., 2001). There is overlap in brain regions subserving self-referential processing and cognitive control - the dlPFC and anterior cingulate subserve both, and are suggested to contribute to excessive control over appetite and food reward in AN (Bischoff-Grethe et al., 2013; Cowdrey et al., 2011; Kaye et al., 2009). These results suggest that RSNs involving self-referential processing and cognitive control may be dysfunctional in AN (Cowdrey et al., 2012).

A subsequent study of both AN and BN, supported these results, reporting increased synchrony between the ACC and precuneus, suggesting increased DMN activity may be present across ED diagnoses. Moreover, this synchrony correlated with body-image concern (Lee et al., 2014). Such processes likely reflect ED specific rumination, concerned with control of eating, shape, and weight (Park et al., 2011, 2012; Rawal, Park, & Williams, 2010; Rawal, Williams, & Park, 2011).

Subsequent studies have also reported increased connectivity in the DMN (Boehm et al., 2014; Lee et al., 2014), and changes in the connectivity of regions associated with cognitive control. Increased connectivity of the dlPFC and ventromedial PFC, associated

with higher levels of perseveration on a set shifting task, has been reported (Favaro et al., 2012), as well as reduced connectivity of the inferior frontal gyrus (IFG), part of the cognitive control system of the brain (Kullmann et al., 2014). These alterations likely reflect the excessive cognitive control and disorder-related ruminations seen in AN (Kullmann et al., 2014), which may in turn exacerbate disorder-specific compulsive behaviours.

Consistent with the altered body-image perception characteristic of AN (Fairburn et al., 2003), aberrant connectivity patterns associated with disturbed body image have also been found. Favaro et al (2012) found decreased connectivity in the ventral-visual network in both acute and recovered AN groups, and increased connectivity in the somatosensory network in the acute AN group. These results were correlated with visuospatial abilities, and were suggested to reflect the inability to integrate visual and somatosensory perceptual information that might sustain body image disturbance in AN (Favaro et al., 2012). In addition, a recent unpublished study from our group found decreased connectivity in regions associated with somatosensory and interoceptive processing, including the insula, pre and postcentral gyri, and the fusiform gyrus, in both current and recovered AN (Scaife, Godier, Filippini, Harmer, & Park, under review). Furthermore Amianto et al (2013) found alterations in the cerebellar-parietal network, with hyperconnectivity between the insula and cerebellum in AN, suggested to be related to impairments in body awareness and perception (Amianto et al., 2013).

5.2.3 Resting State Network aberrancies across compulsive disorders

Dysfunction of the DMN has also been the focus of resting state studies of addiction and OCD, indicating parallels in the dysfunction of RSNs across these disorders and AN. In OCD, a number of studies have reported dysfunction in the connectivity of the

DMN (Cocchi et al., 2012; Fitzgerald et al., 2010). Whilst decreased activity was found within the DMN, increased connectivity was found between the DMN with the anterior insula and superior parietal lobule, which represent nodes of the salience and attention networks respectively (Beucke et al., 2014). It was suggested that these results may reflect disengagement with self-referential processes, and increased activity in regions associated with external task engagement in OCD. Decreased self-referential processing may lead to an inability to dissociate the self from the ego-dystonic obsessional impulses inherent in OCD (Beucke et al., 2014)..

Increased connectivity of the DMN has also been reported in addiction (Camchong et al., 2011). It has been suggested that hyperactivity of the insula reported in addiction, promotes engagement of DMN self-referential processing, at the expense of executive network activity, resulting in the preferential processing of affective/motivational stimuli (Sutherland, McHugh, Pariyadath, & Stein, 2012). Aberrancies in insula connectivity are also reported in OCD (Beucke et al., 2014; Cocchi et al., 2012), and hyperactivity of the insula seen in AN in response to disorder-related stimuli, suggested to reflect the increased salience of food cues in AN (Kim, Ku, Lee, Lee, & Jung, 2012). Along with increased activity in networks promoting rumination on disorder-related cognitions, these aberrancies may promote the preoccupation with disorder-related stimuli, and persistence of maladaptive disorder-related behaviours across compulsive disorders.

Studies of rsFC in OCD and addiction have also largely focussed on dysfunctional connectivity between fronto-striatal regions. As mentioned above, the deactivation of this circuitry has been associated with obsessions and compulsions in AN in response to food cues (Rothemund et al., 2011), which may indicate commonalities in the neural circuitry underlying compulsive behaviour across these disorders. Increased cortical-subcortical connectivity has been reported in OCD (Harrison et al., 2009; Sakai et al., 2011), between

frontal regions such as the PFC and OFC, with subcortical regions such as the dorsal and ventral striatum. Abnormalities in fronto-striatal connectivity in OCD are suggested to be associated with impaired capacity to flexibly adjust behaviour (Fitzgerald et al., 2011), deficits of which are also seen in AN (Holliday et al., 2005; Kanakam, Raoult, Collier, & Treasure, 2013; Roberts et al., 2010). Altered connectivity in fronto-striatal circuitry is also seen in addiction, although the directionality remains unclear. A number of studies have reported increased connectivity between frontal and striatal regions (Ma et al., 2010; Wilcox, Teshiba, Merideth, Ling, & Mayer, 2011), suggesting enhanced engagement of reward and motivation circuits, potentially related to the increased incentive salience of drug-related stimuli (Berridge & Robinson, 1998). However, other studies have reported a reduction in connectivity between the NAc and other subcortical regions, with cortical and prefrontal regions (Gu et al., 2010; Motzkin, Baskin-Sommers, Newman, Kiehl, & Koenigs, 2014; Upadhyay et al., 2010), supporting the suggestion that drug addiction is driven by a general reduction in the functioning of reward systems (Koob & Le Moal, 2005), and reduced activity in cognitive control systems (Motzkin et al., 2014). These disparities may be reflective of differing samples (e.g. abstinent vs current users, differing drugs of abuse) and different methodologies (Sutherland et al., 2012).

As discussed in Section 1.7, the OFC forms part of the neural circuitry implicated in compulsive behaviour, and abnormalities in this region can be seen across AN, OCD and addiction. In a study directly comparing individuals with OCD and substance addiction, decreased connectivity was found between the superior and inferior regions of the OFC in both disorders. This was positively correlated with compulsive symptoms in both OCD and substance dependence, suggesting a role for abnormalities in the OFC in the development of compulsive behaviour across disorders (Meunier et al., 2012).

5.2.4 Electrophysiological measures of resting state activity across compulsive disorders

Although most rsFC studies have been conducted using fMRI techniques, electrophysiological techniques such as MEG can also be used to look at the temporal coherence of brain networks. MEG allows the direct measurement of neural activity in the form of magnetic fields elicited by the electrical activity of pyramidal neurons in the cortex (See Appendix 5.1 for a brief introduction to MEG). This gives MEG a high level of temporal resolution compared to fMRI, as activity can be measured in real time (Baillet, Mosher, & Leahy, 2001).

Brain patterns form wave shapes that are commonly sinusoidal, and the brain state of the individual may make certain frequencies more dominant. Brain waves have been categorized into four basic groups: delta: 0.5–4 Hz; theta: 4–8 Hz; alpha: 8–13 Hz; beta: 13-30 Hz (Jauregui-Lobera, 2012). These neural oscillations play an important role in coordinating neural activity, and are thought to be closely involved in network activity (Brookes, Hale, et al., 2011; Womelsdorf et al., 2007).

Whilst to date there are no published MEG investigation of AN, two resting state studies using electroencephalography (EEG) have been reported. EEG is closely related to MEG, and is the recording of electrical brain activity along the scalp that gives rise to the magnetic fields recorded in MEG. Resting state EEG studies in AN have reported disturbances in alpha/beta rhythms, associated with the underweight state only (Hatch et al., 2011; Rodriguez et al., 2007), as well as some stable and generalised disturbances in theta activity, suggested to reflect underlying anxiety sensitivity/vulnerability that may predate AN onset, and persists after recovery (Hatch et al., 2011)

Few resting state studies have used MEG to investigate compulsive disorders at rest. A resting state MEG study looking at OCD patients emphasised the fronto-temporal dysfunction often reported in OCD (Maihofner et al., 2007), and a study of pathological gamblers found altered interaction between regions in the paralimbic circuitry, suggested to reflect aberrancies in self-awareness and self-evaluation in these individuals (Romer Thomsen et al., 2013). Resting state EEG studies in OCD and substance dependence have shown fairly inconsistent results. Whilst frontal hyperactivation has been indicated by some studies in OCD (Koprivova et al., 2011; Velikova et al., 2010), others have reported decreased alpha/beta rhythms in frontal cortical regions (Pogarell et al., 2006). The latter was correlated with measures of obsessions and compulsions, suggesting a link between dysfunctional electrophysiological rhythms in frontal regions, and symptomology in OCD (Pogarell et al., 2006). Another study reported increased delta activity in the insula, and increased beta activity in frontal, parietal and limbic regions, supporting suggested dysfunction of cortico-subcortical connections in OCD (Velikova et al., 2010). In substance dependence, increased beta activity has been found in a number of regions in male alcoholics and their offspring (Rangaswamy et al., 2002; Rangaswamy et al., 2004), suggesting a potential biomarker for vulnerability to alcoholism (Rangaswamy et al., 2004). Correlations have also been reported between changes in spontaneous EEG rhythms and clinical variables such as length of addiction, hallucinations, and family history of alcoholism, suggesting both state and trait changes in cortical rhythms are associated with addiction (Coutin-Churchman, Moreno, Anez, & Vergara, 2006). Behavioural addictions have also been associated with changes in electrophysiology at rest. For example, exercise addiction has been linked to increased left frontal activity (Gapin, Etnier, & Tucker, 2009), and internet addiction with increased beta/decreased gamma rhythms (Choi et al., 2013).

MEG has a much higher temporal resolution than fMRI, which has potential advantages for identifying aberrancies related to the temporal coherence of RSNs. In addition, unlike EEG, magnetic fields are not distorted by inhomogenous conductivity in the head (i.e the disruption of conductivity from the skull and scalp), giving MEG a higher spatial resolution that EEG (Brookes, Woolrich, et al., 2011). Combined with the larger number of sensors utilised in MEG, this makes projection into source space more successful in MEG compared to EEG. In support of this, Independent Components Analysis (ICA) of resting MEG data has been shown to identify RSNs with a similar spatial structure to RSNs derived using fMRI techniques (Brookes, Woolrich, et al., 2011; Lu & Stein, 2014). The current study will utilise this technique to further investigate aberrancies in neural networks in individuals with current and past AN compared to healthy controls, and the association this may have with self-reported compulsivity, measured by the Self-Starvation Questionnaire developed in Chapter 3.

5.3 Aims

- To investigate aberrancies in the temporal coherence of RSNs in AN (current and past), compared to healthy controls.
- To investigate whether aberrancies in resting state neural networks in AN are state or trait-related, by looking at differences between those with current and past AN.
- To investigate whether aberrancies in the connectivity of resting state neural networks in AN are related to self-report measures of compulsivity.

5.4 Hypotheses

- It is hypothesised that individuals with current and past AN will show aberrancies in the temporal coherence of neural networks associated with rumination and cognitive control, and that this will be associated with self-reported levels of compulsivity.

5.5 Methods

5.5.1 Participants

Forty-two participants were recruited for three experimental groups; current AN (AN-C, n=12), recovered AN (AN-R, n=14), and healthy controls (HC, n=16). General exclusion criteria included age <18 or >60, insufficient English language comprehension, male sex, left-handedness, and any contraindication to having a Magnetic Resonance Imaging (MRI) scan (head injury, neurological or any other severe medical illness, pregnancy, metal implants of any kind). The specific inclusion and exclusion criteria outlined below was designed to enable valid differentiation between the AN groups and the healthy controls. Ethical permission for this study was obtained from the NRES South Central – Oxford A Research Ethics Committee (See Appendix 4.1).

5.5.1.1 AN-C Group

Inclusion criteria for the AN-C group included a current diagnosis of restrictive AN according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), as indexed by the Structured Clinical Interview for DSM-IV (SCID), the Eating Disorder Examination (EDE), and current BMI. Participants with a history of or current diagnosis of binge/purge type AN or BN were excluded. Four participants were on both antidepressant (SSRI or SNRI) and atypical antipsychotic medication, and two were taking just antidepressant (SSRI) medication. Seven participants currently met the criteria for a mood disorder, 7 met the criteria for current Generalised Anxiety Disorder (GAD), and two met the criteria for current OCD. Three participants reported previous but not current episodes of depression and 1 participant reported a previous episode of PTSD. One participant was excluded after screening as she reported a history of binge/purge AN.

5.5.1.2 AN-R Group

Inclusion criteria for the AN-R group included a past diagnosis of restrictive AN according to the DSM-IV as assessed by the SCID. Participants with a history of binge/purge type AN or BN were excluded. In addition, participants must have maintained a BMI between 18.5 and 25 for the previous 12 months (assessed by self-report), score within 1 SD of the EDE and EDE-Q global mean scores for young women, and not meet current criteria for any DSM-IV disorder as assessed by the SCID. Whilst none of the AN-R participants currently met criteria for depression, 12 had previously met the criteria for depression, and 5 were currently taking antidepressant medication. In addition, 3 participants had previously met the criteria for GAD, and 1 for OCD. One participant was excluded after screening as she reported a history of BN.

5.5.1.3 HC Group

Inclusion criteria for the HC group included a current BMI between 18.5 and 25, no first degree relative with a current or past ED diagnosis (assessed by self-report), no current or past diagnosis of a DSM-IV disorder (assessed by the SCID), scores within 1 SD of the EDE and EDE-Q mean scores for young women. Four participants were excluded after screening due to violation of one of the above criteria.

5.5.2 Procedures

Participants were initially sent an information sheet (See Appendix 4.2) and description of the study by email. They were then asked to complete a number of screening questions, and an online version of the EDE-Q to ensure they met the criteria for the study. Participants were then invited to an initial screening session at the Warneford Hospital (as described in Section 4.5.2).

Participants subsequently attended two more sessions in order to complete the MEG scan at the Oxford Centre for Human Brain Activity (OHBA), and the Oxford Centre for Magnetic Resonance Imaging (OCMR) for an MRI structural scan. Participants were asked not to eat for 8 hours prior to the MEG scan. Previous studies have suggested that food deprivation may increase the activation of the appetitive motivational system (Mauler, Hamm, Weike, & Tuschen-Caffier, 2006). As such, it is predicted that in the fasted state psychopathological processes will be most naturalistic for those with current AN, and most comparable across groups. Following completion of the study, participants were paid £7.50 per hour in compensation for their time.

5.5.3 Measures

During the screening session, participants completed the measures described in Section 4.5.3. To assess subjective states before the MEG scan, participants completed a series of 100mm visual analogue scales (VAS; see Appendix 4.4) assessing in the moment mood (happiness, sadness, anxiety), appetite related variables (hunger, thirst, fullness, desire to eat), and ED related variables (current body image, fear of gaining weight).

5.5.4 MEG Scan

MEG data was acquired using an Elekta 306 channel MEG system. On arrival participants were asked to complete VAS scales to assess current mood state, and time of previous intake of food and drink was noted down. Participants were also screened for any contraindications to MEG. Participants were then shown the MEG scanner, and asked to sit in the scanner briefly to check for any artefacts in the MEG signal. Once out of the scanner room, two electrodes were placed next to the left eye to record EOG (Electrooculography) data, two were placed on the wrist to record ECG (Electrocardiogram) data, and a grounding coil was placed in the centre of the forehead.

Four standard Elektra Head Position Indicator (HPI) coils were attached at known locations on the head using double sided tape – two were placed on the forehead, and two behind each ear. The position of the HPI coils, and head shape digitisation was determined with 100+ head points made using a Polhemus 3D digitiser. The HPI coil locations are then plugged into the system, and allow the coil locations (head position) to be determined in relation to the MEG sensor array. This allows for co-registration with MRI and head tracking during the scan.

5.5.5. Resting State Protocol

Participants were then asked to fixate on a centrally positioned fixation cross for 6 minutes whilst resting state data was recorded. The fixation cross was presented via Presentation software package projected onto a screen via Panasonic DLP based projector PT-D7700E (viewing distance 1.2 m, screen size 54.5 x 43 cm, resolution 1280 x 1024). Participants were instructed to keep their eyes open and direct their gaze towards the fixation cross, whilst letting their mind wander. Data was re-recorded if participants fell asleep, or had their eyes closed for a significant amount of time.

5.5.6. MRI Structural Scan

An MRI structural scan was taken using the 3.0 Tesla TIM Trio scanner at the OCMR. 3D high-resolution T1-weighted MR images were acquired for subject alignment using a MPRAGE sequence (174x192x192 matrix, voxel resolution 1mm3, TR=2040ms, TE=4.7ms, inversion time (TI)=900ms, acquisition time=6 min). Upon arrival participants were asked to complete the MRI safety screening form to ensure they did not present with any contraindications to the MRI, and were asked to remove any metal from their person. Participants were shown into the scanner control room and introduced to the radiographer who conducted safety checks with the participant. The participants were then taken into

the magnet room and asked to lay head first in the scanner bore. The radiographer placed the head coil on participants and attached a viewing mirror. The radiographer left the magnet room and communicated with the participants through the intercom. Structural MRI was acquired at the end of the two functional MRI sequences.

5.5.7 Data Analysis

5.5.7.1 Demographic and Questionnaire Data

Demographic, questionnaire and VAS scale data were analysed using one way ANOVAs in SPSS.

5.5.7.2 Pre-processing of MEG data

MaxFilter 2.2 (Elekta Neuromag, 2010) was first applied to the Neuromag data. This mathematically transforms data into a set of virtual sensors, and implements a spatial signal space separation (SSS) algorithm to remove external noise from the MEG recordings, by supressing any activity that does not stem from these virtual channels. In addition to SSS denoising, and as part of the SSS algorithm, MaxFilter is able to correct for movements and differences in head position between subjects, re-projecting the data onto the MEG sensors as if the data had been recorded with the head in a different position.

Data was then pre-processed using the OHBA Software Library (OSL) Preprocessing Tool (OPT), which is a fully automated pipeline. Data was converted into SPM format and downsampled to 250Hz. Independent Component Analysis (ICA) was then used to remove certain artefacts, such as eye-blinks, ECG and line noise, which can be separated from the genuine MEG data and removed. Data was high-band pass filtered to

remove frequencies below 0.1Hz, and artefact time periods and bad channels were removed from the data.

5.5.7.3 Analysis of MEG Resting State Networks

Analysis and identification of RSNs was performed using the OSL Resting state ICA pipeline (as described in Brookes et al., 2011). For speed and efficiency, structural MRIs were resampled to an 8mm grid using FLIRT in FSL. Structural MRIs were then coregistered to the MEG data for each subject. MEG data was then separately frequency filtered into alpha (8-13Hz) and beta (13-30Hz) bands and projected into source space using a scalar beamformer. Beamforming constructs a spatial filter, which is then applied to the sensor data to reconstruct the signal at each point of the grid, whilst minimising the variance from all other locations. Data from each source location are given by multiplying the beamformer weights vector by the original sensor data. This is repeated from each grid point to obtain a whole-brain source reconstruction. Covariance matrices were generated independently for each frequency band, using all 360s of recorded data on a subject-by-subject basis. All covariance matrices were regularised using a regularisation value of 4× the minimum singular value of the unregularised matrix. Voxels were placed on a regular 8-mm grid spanning the entire brain and source orientation at each voxel was based on a nonlinear search for maximum projected signal-to-noise ratio.

Following beamformer projection, source-space signals were normalised by an estimate of projected noise and a Hilbert transform was applied to each voxel time course to derive the "analytic signal". The absolute value of the analytic signal was computed to yield an amplitude envelope of oscillatory power, termed the "Hilbert envelope". The Hilbert envelope at each voxel was down-sampled to an effective sampling rate of 1 Hz. Source space envelope data were smoothed spatially (FWHM 4 mm) and transformed to

standard (MNI) space using FMRIB's Linear Image Registration Tool (FLIRT) in FSL, and the voxel size was resampled to an 8-mm grid. Power envelopes were downsampled using a filter length of 8 seconds. Datasets from all subjects were concatenated in the time dimension across subjects.

Temporal ICA was applied to the concatenated dataset using the fastICA (research.ics.tkk.fi/ica/fastica) algorithm, in which the data were reduced to 25 dimensions using an Independent Components Analysis. These 25 components were then converted into correlation spatial maps by estimating the Pearson's correlation coefficient between each independent time course and the down-sampled amplitude envelope time-course, concatenated across subjects, associated with each voxel. This resulted in maps showing the extent to which each voxel correlates with each component, providing a spatial distribution for each component.

A voxel-wise General Linear Model (GLM) was implemented to investigate group differences in the temporal coherence of the identified ICA components with the rest of the brain. This is done by concatenating the components back into individual subject time courses and then applying a GLM approach. The GLM matrix design has a regressor for each condition of interest (each group), with ones indicating those trials that belong to the condition of interest, and zeros otherwise. This denotes the experimental group each participant belongs to. The GLM allow the identification of, within each participant's data set, subject-specific temporal dynamics and spatial maps that are associated with each ICA component. A linear model is fit between the ICA components and the individual subject time courses, giving the temporal dynamics for ICA component for each subject. A linear model is then fit between the resulting subject-specific component time-course matrices and the individual data sets to determine subject-specific component spatial maps. These maps are then collated across participants, giving one per group for each identified

component. Contrasts are then set up to perform voxel-wise independent sample t-tests to investigate statistically significant differences between groups in the temporal coherence of these group-specific ICA component maps with the rest of the brain. Six contrasts were investigated: AN-C>HC, HC>AN-C, AN-R>HC, HC >AN-R, AN-C>AN-R, and AN-R>AN-C. Non-parametric permutation testing (1000 permutations) was used with threshold free cluster enhancement (TFCE), and a corrected cluster significance threshold of p=.05. This results in spatial maps showing significant between-group differences which can be viewed in FSL.

5.6 Results

5.6.1 Demographics

Table 5.1 summarises the demographic and psychological characteristics of the three experimental groups. There were no differences in age, years in education or sensitivity to reward (SPSRQ) across the three groups. There was no difference between the AN-C and AN-R group in lowest BMI, however the AN-C group had a significantly longer duration of illness and later age of onset of illness than the AN-R group. The AN-C had significantly lower BMI and lower experiential avoidance scores, and significantly higher scores on measures of ED psychopathology, depression, and state anxiety than the AN-R and HC groups. The AN-C group had significantly higher scores on obsessive compulsive symptoms (OCI-r) and sensitivity to punishment (SPSRQ) than the HC group. Both the AN-C and AN-R group had significantly higher scores on a measure of past eating disorder obsessions and preoccupations (YBC-EDS-SRQ Past), and trait anxiety (STAI-trait), than the HC group. The AN-R group did not differ to the HC group in scores of ED psychopathology (EDE, EDE-Q, CIA, SS, YBC-ED-SRQ current), BMI, experiential avoidance (AAQ), depression (BDI), or state anxiety (STAI state).

Table 5.1 Demographic and psychological characteristics.

	AN-C (n=12)		AN-R (n=14)		HC (n=16)		Significance (p two tailed)	Pairwise post hoc group comparisons
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Age	29.58	5.84	27.07	6.49	24.25	5.72	.078	---
BMI	15.73	1.99	20.94	1.63	21.26	1.96	<.001	AN-R, HC>AN-C
Lowest BMI	12.98	1.18	13.8	1.23	-	-	.100	---
Age of Onset	20.33	5.74	16.5	2.1	-	-	.015	AN-C>AN-R
Duration of AN	10.25	5.2	5.75	4.15	-	-	.010	AN-C>AN-R
NART	114.67	7.43	114.57	6.77	108.63	7.13	.039	HC< AN-R
Years in Education	18.17	4.26	18.64	2.66	16.81	2.23	.286	---
EDE	3.07	1.50	0.74	0.61	0.23	0.20	<.001	AN-C >AN-R, HC
EDE-Q	3.20	1.71	0.95	0.85	0.47	0.32	<.001	AN-C>AN-R, HC
AAQ	33.83	12.27	48.0	9.20	56.38	8.34	<.001	AN-R, HC>AN-C
SPSRQ Punishment	15.75	6.08	12.07	4.70	8.56	3.97	.002	AN-C>HC
SPSRQ Reward	8.67	3.89	8.86	4.28	9.44	3.29	.852	---

	AN-C (n=12)		AN-R (n=14)		HC (n=16)		Significance (p two tailed)	Pairwise post hoc group comparisons
BIS	53.50	6.86	61.57	9.72	55.94	11.36	.102	---
CIA	29.67	14.01	7.93	6.5	1.81	2.32	<.001	AN-C>AN-R, HC
OCI-r	20.42	16.40	10.79	6.45	6.31	7.09	.004	AN-C> HC
BDI	28.25	18.22	6.36	6.43	3.25	4.48	<.001	AN-C> AN-R, HC
STAI-State	49.42	13.39	34.43	5.45	26.94	6.55	<.001	AN-C>AN-R, HC
STAI-Trait	60.42	13.45	45.21	10.56	32.88	9.74	<.001	AN-C>AN-R> HC
YBC-EDs-SRQ Current	15.42	7.76	3.79	3.95	0	0	<.001	AN-C>AN-R, HC
YBC-EDs-SRQ Past	24.08	5.16	23.82	5.30	0	0	<.001	AN-C, AN-R> HC
SS	49.17	26.82	5.29	8.36	0.25	0.77	<.001	AN-C>AN,-R HC

Note: BMI = Body Mass Index; NART = National Adult Reading Test; EDE= Eating Disorder Examination; EDE-Q = Eating Disorder Examination Questionnaire; AAQ = Acceptance and Action Questionnaire; SPSRQ = Sensitivity to Punishment and Sensitivity to Reward Questionnaire; BIS = Barratt Impulsiveness Questionnaire; CIA = Clinical Impairment Assessment; OCI-r = Obsessive Compulsive Inventory Revised; BDI = Beck Depression Inventory; STAI = State Trait Anxiety Inventory ; YBC-EDS-SRQ = Yale-Brown-Cornell Eating Disorder Scale Self-Report Questionnaire; SS = Self-Starvation Scale. --- denotes no significant difference.

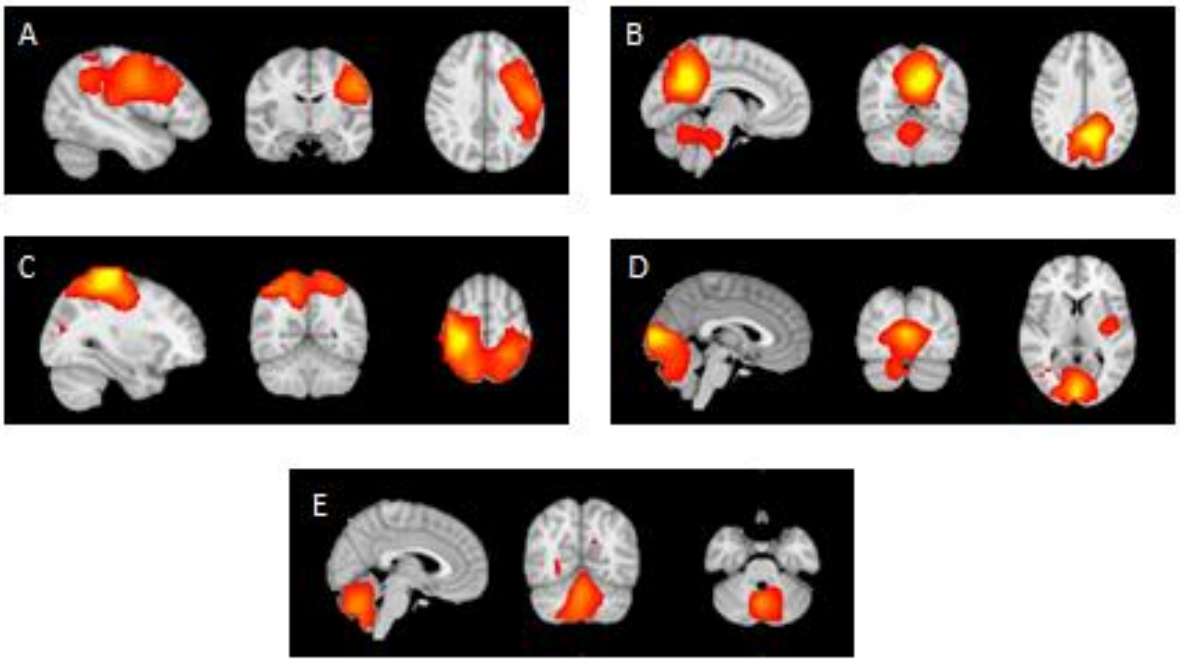
5.6.2 VAS Scales

A series of one-way ANOVAs were used to examine differences in VAS scales of mood, appetite and ED-related variables prior to the MEG scan across groups. There were significant group differences in happiness ($F[2,41]=3.684$, $=.034$), hunger ($F[2,41]=5.225$, $p=.010$), desire to eat ($F[2,41]=4.475$, $p=.018$), and fear of fatness ($F[2,41]=15.766$, $p<.001$). Bonferroni corrected post-hoc analysis indicated significantly higher happiness, hunger, and desire to eat in the HC compared to AN-C group ($p<.05$). Fear of fatness followed a pattern of AN-C>AN-R>HC ($p<.05$). The means and standard deviations for VAS scales across groups are shown in Appendix 5.2

5.6.3. Independent Components Analysis

A Temporal ICA (described in Section 5.5.7.3) was used to define 25 temporally independent components in the beta and alpha frequency bands of the resting state MEG data. Of these, 5 were identified as known RSNs (See Figure 5.1) previously found using MEG, and shown to be spatially similar to RSNs commonly found using fMRI (Brookes, Woolrich, et al., 2011). The RSNs of interest included the left-fronto parietal, medial parietal, motor, and visual networks in the alpha band, and the cerebellum in the beta band.

Figure 5.1 RSNs obtained from ICA.



(A) Left fronto-parietal network (α); (B) Medial Parietal Network (α); (C) Sensorimotor Network (α); (D) Visual Network (α); (E) Cerebellum (β). Note: (α) = alpha band; (β) = beta band.

5.6.4. GLM results

A GLM was applied to investigate group differences in the temporal coherence of the identified RSNs with the rest of the brain. No significant regions were identified in any of the contrasts, providing no evidence for significant differences in the temporal coherence of the identified RSNs across the three groups.

5.6.5. Follow up analyses using an fMRI Basis Set

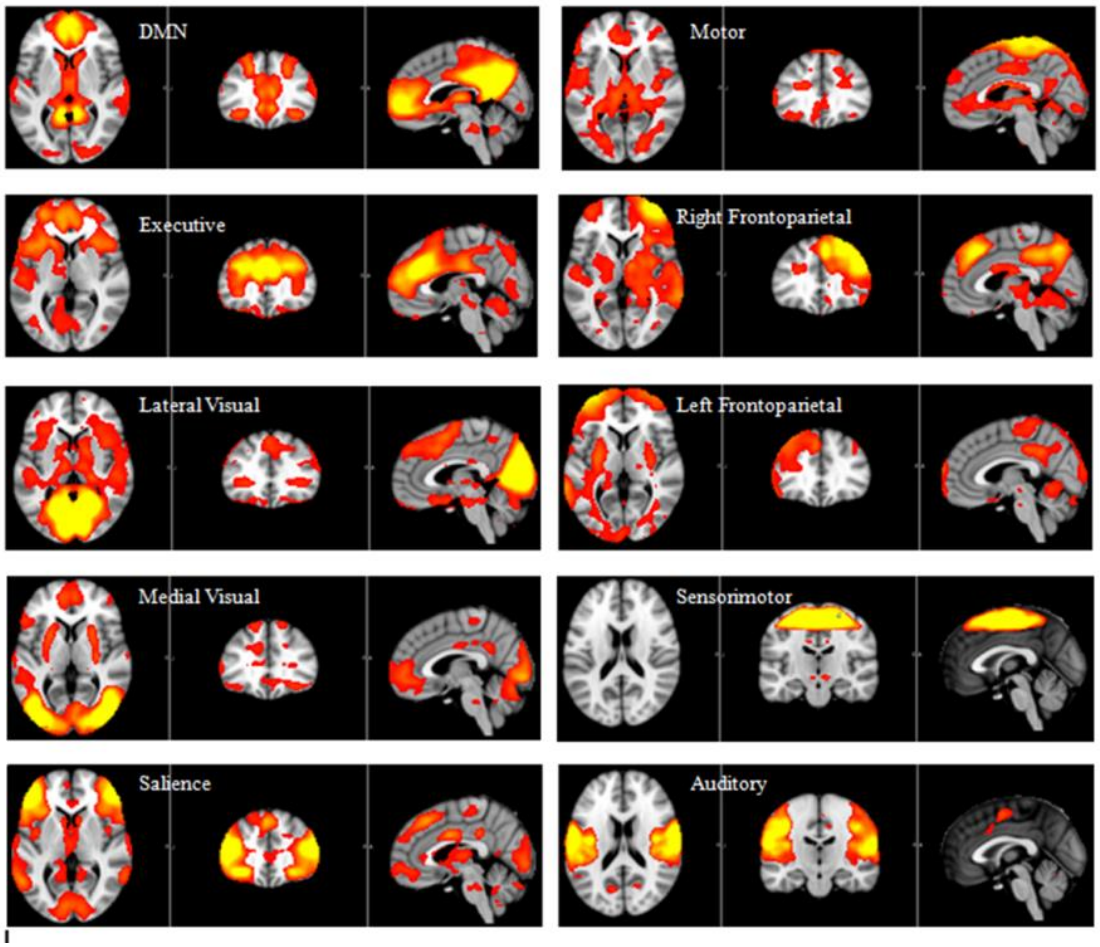
In light of the null findings of the above analyses, a second GLM analysis was performed using an fMRI basis set. This allows investigation of group differences in the temporal coherence of the neural activity measured using MEG, with RSN components derived from an ICA of fMRI data. The fMRI RSN components were from an fMRI study using the same participants, and following the same experimental protocol in the MRI

scanner as used in MEG in this study (Scaife et al., under review). The GLM model was identical to that described in Section 5.5.7.3, replacing the MEG ICA components with those derived from the fMRI data. Analysis of this fMRI data was carried out using MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components, part of FSL http://www.fmrib.ox.ac.uk/fslmelodic/; Beckmann, DeLuca et al. et al., 2005). Figure 5.2 shows the 8 RSNs identified in this analysis: The DMN, medial visual, lateral visual, auditory, sensory-motor, executive control, and fronto-parietal (right and left) networks. These networks corresponded to RSNs which have been described previously and show with high stability over time (Beckmann, DeLuca, Devlin, & Smith, 2005).

Using this fMRI basis set, no regions were identified to show significant group differences in any of the contrasts. Again this provides no evidence for significant differences in the temporal coherence of neural activity measured by MEG, with the RSNs identified using fMRI across the three experimental groups in this study.

Figure 5.2. RSNs obtained using ICA in fMRI data (Scaife et al., under review).

Note: DMN = Default Mode Network



5.6.6 Summary of results

- No group differences were found in the temporal coherence of RSNs identified from MEG resting state data using an ICA, in current or recovered AN, compared to healthy controls.
- No group differences were found in the temporal coherence of MEG activity with RSNs identified using fMRI in the same sample.

5.7 Discussion

In this study, no alterations in the temporal coherence of RSNs identified from resting state MEG data were found in individuals with experience of AN (current or past) compared to healthy controls. As such, it was not possible to investigate an association between RSN dysfunction and measures of compulsive behaviour in AN. An additional analysis using a basis set of fMRI RSN components derived from the same participants also indicated no significant group differences in the temporal coherence of the MEG activity with these components. These results conflict with the hypotheses of this study, and with previous fMRI investigations of rsFC in AN, in which aberrancies in networks associated with rumination, cognitive control and body-image perception have been reported.

As discussed in Chapter 4, null results should be interpreted with caution, and there are two possible explanations for this result: firstly, the null hypothesis (i.e. that there are no group differences) may be correct, secondly we fail to reject the null hypothesis when it is in fact false (Aberson, 2002). This second possibility often occurs when a study has low statistical power, as is the case in the majority of neurobiological studies in psychiatric populations, which often use small sample sizes due to financial and practical constraints (Button et al., 2013). Similarly, as this was an exploratory investigation of RSNs in AN using a novel technique, the sample size used was relatively small, whilst being similar to many neuroimaging studies in this population, and as such a power analysis was not conducted prior to determination of the sample size. In light of these possible power issues, whilst the null hypothesis was not rejected in this case, nothing can be concluded regarding the alternative hypothesis (that there are group differences). Whilst published fMRI studies of RSN dysfunction in AN have suggested alterations in the rsFC of a

number of networks, the low statistical power, as well as methodological differences, in these studies may underlie the inconsistency and variability of these results. For example, both increased and decreased connectivity of the DMN have been reported in AN (Cowdrey et al., 2012; McFadden, Tregellas, Shott, & Frank, 2014). Future studies would benefit from larger sample sizes, and consequently higher statistical power to detect changes in MEG RSNs in AN.

Whilst MEG has unparalleled temporal resolution in measuring neural activity, its spatial resolution is much lower than that of fMRI (Baillet, Friston, & Oostenveld, 2011). Although the analysis used in this study has previously been shown to successfully identify spatially similar RSNs to those consistently found using fMRI (Brookes, Woolrich, et al., 2011), it is possible that in combination with a small sample size, the spatial resolution was not adequate to detect group differences in source-space in the identified RSNs. Indeed, in a parallel fMRI study using the same sample, and the same experimental protocol, (from which the fMRI basis set described in Section 5.6.5 was derived), differences were detected in the auditory and lateral visual network in the AN-C and AN-R group compared to controls (Scaife et al., under review). This raises the possibility that MEG may require larger sample sizes than fMRI to detect subtle group differences in the temporal coherence of spatial RSNs.

Additionally, as it is recorded from the scalp, MEG is much better at detecting activity from cortical regions than subcortical regions, as spatial resolution decays with distance from the MEG sensors (Hillebrand & Barnes, 2002). Whilst dysfunction in frontal and cortical regions, associated with rumination and cognitive control, has been reported in AN, it may be that important differences lie in subcortical regions, the activity of which MEG may not be sensitive to. If, as suggested in Chapter 1, compulsive behaviour in AN and across compulsive disorders is reflected in dysfunction in fronto-striatal circuitry,

MEG may not be suited to detecting these aberrancies. Indeed, decreased functional connectivity of the dorsal striatum has been reported in AN, and linked to compulsive behaviour (Favaro et al., 2014).

As suggested above a limitation of this study was the small sample size, which may have limited the ability to find statistically significant differences in the data. Another methodological limitation of note was that a number of participants in the AN groups had comorbid anxiety or depression diagnoses, and so were taking serotonergic antidepressants and/or antipsychotic medications. Antidepressant and antipsychotic medications have been shown to alter neural activity measured by MEG (Korostenskaja & Kahkonen, 2009; Mendez et al., 2012), and so the effects of these medications, or indeed comorbid diagnoses, on our results cannot be ruled out.

5.7.1. Conclusions

The results of this study do not support previous findings of dysfunction in RSNs associated with cognitive control, rumination and body-image disturbance in AN. However, methodological limitations, such as low statistical power and medication status, mean we cannot conclude that these aberrancies do not exist. Additionally, limitations in the spatial resolution of MEG may have further reduced the ability to detect significant differences in combination with low statistical power. Future studies would benefit from larger sample sizes free from medication in order to investigate RSN activity in AN using MEG.

6. General Discussion

6.1 Overview of thesis

Chapter 1 highlighted the need for translational research in AN to further our limited understanding of the processes underpinning the disorder, and to develop novel treatment avenues, which are greatly needed in AN. This thesis aimed to address this by investigating the compulsive nature of behaviour in AN, and the mechanisms that might underlie the development of this behaviour. In light of similarities in compulsive disorder-specific behaviour across diagnoses, a transdiagnostic theory of compulsivity has been proposed, suggesting that this construct of behaviour is evident to varying degrees across disorders (Robbins et al., 2012). Conceptualising compulsivity in this way allows us to make a number of hypotheses regarding the underlying mechanisms of persistent self-starvation in AN, which have been used to guide the research reported in this thesis.

There is a paucity of research investigating the compulsive nature of behaviour in AN, despite increasing suggestion of parallels with other compulsive disorders such as OCD and substance dependence (Barbarich-Marsteller et al., 2011; Kaye, Wierenga, Bailer, Simmons, Wagner, et al., 2013; Park et al., 2014; Scheurink et al., 2010; Steinglass & Walsh, 2006; Walsh, 2013; Zink & Weinberger, 2010). Chapter 1 discusses how potential behavioural mechanisms of compulsivity (i.e. excessive habit formation), and underlying neurobiological markers (i.e. cortico-striatal neurocircuitry dysfunction), may relate to compulsive behaviour across disorders including AN. Mechanisms reflecting compulsive and habitual control of behaviour in AN may help explain the persistence of the disorder, and high relapse rates. In light of this, the overall aim of this thesis was to explore a transdiagnostic perspective on compulsivity in relation to behaviour in AN, in order to help delineate behavioural and neural underpinnings of persistent weight loss

behaviour in AN. Four studies were carried out using different methodologies to explore the potential transdiagnostic relevance of compulsive weight-loss behaviour, at the level of subjective symptomology, behaviour and neurobiology. The principal findings of each study are outlined below.

6.2 Overview of findings

The study in Chapter 2 explored the validity of suggested parallels between AN and substance dependence with a qualitative investigation. A thematic qualitative analysis suggested that some individuals with AN view the compulsive nature of their behaviour as central to the maintenance of their disorder, and many see it as a significant barrier to recovery. The themes that emerged from the qualitative analysis were shown to map onto the DSM-V criteria for SUDs, with similarities in the lack of control over ceasing behaviour, the increasing nature of compulsions over time, the avoidance of negative psychological states, and the significant functional impairment seen in both disorders. The similarities shown between these themes and the criteria for SUDs supports increasing suggestion of the parallels in the compulsive disorder-specific behaviours characteristic of AN and substance dependence (Barbarich-Marsteller et al., 2011; Kaye, Wierenga, Bailer, Simmons, Wagner, et al., 2013; Park et al., 2014; Scheurink et al., 2010; Zink & Weinberger, 2010), and the transdiagnostic nature of compulsivity (Robbins et al., 2012).

In Chapter 3, the behavioural parallels reported between AN and addiction in Chapter 2 were utilised to aid the development of measures capturing compulsive weight-loss behaviours. Two novel self-report measures were created by adapting the questions of the Yale Food Addiction Scale (YFAS) (Gearhardt et al., 2009), for compulsive self-starvation and excessive exercise behaviour. The YFAS is modelled on the DSM-IV criteria for substance dependence, and as such allowed further investigation of the transdiagnostic

relevance of compulsivity across disorders. The new Self-Starvation Scale (SS) and Compulsive Exercise Scale (CES) were first validated in a community sample, and were shown to have good criterion-related validity, internal consistency, and test-retest reliability in this sample. Whilst scores on the SS were shown to be independently predictive of ED symptoms measured by the EDE-Q, scores on the CES were not predictive of ED symptomology. This may reflect the presence of compulsive exercise independent of disordered eating in the community sample, which included those who take part in competitive sports. However, the CES was found to be independently predictive of ED-related clinical impairment (CIA scores) in this sample, suggesting that the presence of compulsive exercise may lead to increased ED-related impairment.

Subsequent validation in a sample of individuals with experience of AN (current and past) replicated the psychometric properties of both scales. The predictive ability of the SS in this sample was particularly strong for those with a current diagnosis of AN, suggesting this measure may be particularly useful in clinical samples, in which self-starvation behaviour is likely to be most evident. In addition, the predictive ability of the SS was particularly strong for the restraint subscale of the EDE-Q, reflecting the rigid rule-driven behaviour captured by the SS. However, the CES was unable to predict ED symptoms in this sample, or clinical impairment as seen in the community sample. This may be reflect generally high levels of clinical impairment in individuals with AN, which may be independent of compulsive exercise behaviour. Equally, compulsive exercise may still be present in those recovered from AN who no longer show ED psychopathology. The results this study support the efficacy of using the criteria of dependence in capturing compulsive weight-loss behaviour, particularly self-starvation behaviour, and suggest that compulsivity, as a construct of behaviour, may have transdiagnostic application, on which disorder-specific themes are superimposed.

The results reported in Chapters 2 and 3 provide preliminary support for the parallels between the compulsive drug-seeking behaviour in SUDs, and weight-loss behaviour in AN. However, these chapters are limited by their reliance on self-report, which may be particularly relevant for individuals with AN, who show low interoceptive awareness (Fassino et al., 2004), and as such may inaccurately report their feelings and behaviours. Chapter 4 aimed to address this by using validated experimental tasks to investigate the neuropsychological mechanisms which may underpin the persistence of weight-loss behaviours in AN.

As discussed in Chapter 1 (see Section 1.9), emergent evidence suggests that dysregulation of the balance between the goal-directed and habitual systems of behavioural control may provide a mechanism by which the development of well-entrenched, compulsive behaviours can occur across disorders. A tendency to rely on habits in instrumental learning has been reported across compulsive disorders such as substance dependence, OCD and BED (Gillan et al., 2015; Gillan et al., 2013; Gillan et al., 2011; Sjoerds et al., 2013; Voon et al., 2014), and has been suggested as a potential mechanism for the development of compulsive and persistent weight-loss behaviour in AN (Steinglass & Walsh, 2006; Walsh, 2013). Initial support for this comes from studies showing aberrancies in the neural circuitry (cortical-striatal circuits) associated with habitual control of behaviour in AN (Rothemund et al., 2011).

Chapter 4 aimed to investigate whether a tendency to rely on habits in learning is also present in individuals with current and past AN. Two validated outcome-devaluation tasks, previously used to show the persistence of habits in OCD and substance dependence (Gillan et al., 2015; Gillan et al., 2013; Gillan et al., 2011; Sjoerds et al., 2013), were employed in this study. These tasks measure the persistence of responses for which the

outcomes are no longer valuable, which may reflect the persistence of compulsive behaviours despite adverse consequences.

The behavioural results reported in Chapter 4 showed no evidence for a tendency to develop appetitive (reward-based) or aversive (avoidance-based) habits in individuals with current or past AN using two established outcome devaluation tasks. These results were followed up by Bayesian analyses, which supported the increased likelihood of the null hypothesis (i.e. that there are no group differences), compared to the alternative hypothesis (i.e. there are group differences). Whilst this study suggests a pervasive vulnerability to develop habits may not be evident in AN, this does not rule out the possibility that disorder-specific behaviours may become habitual over time. It was further suggested that the aberrantly rewarding nature of dietary restriction and weight-loss in AN, coupled with an enhancement of habits during starvation, may promote a transition to habitual control of disorder-specific behaviour in AN. This is supported by preliminary evidence of deficits in reversal learning (a paradigm measuring cognitive flexibility, a rigid cognitive style which may contribute to compulsivity) in AN, using food-based stimuli (Hildebrandt et al., 2015), with only subtle deficits reported using disorder-neutral stimuli (Sarrar et al., 2011).

The results of Chapter 4 were surprising considering the aberrancies reported in regions of the cortico-striatal circuitry in AN (Cowdrey et al., 2011; Favaro et al., 2014; Frank et al., 2012; Frank et al., 2013; Rothemund et al., 2011; Uher et al., 2004; Wagner et al., 2007), suggested to be involved in goal-directed and habitual control of behaviour (de Wit et al., 2012; Gillan et al., 2015; Voon et al., 2014). However, these studies have used symptom-provocation paradigms, and as such may reflect the development of disorder-specific habits, as suggested above.

Aberrancies in the functioning of neural networks at rest (independent of the task paradigm) have also been investigated in AN using fMRI. Temporal correlation of BOLD signals across brain regions are used to identify resting state neural networks (RSNs), which are important for information processing (Biswal et al., 1995). Increased activity of RSNs associated with rumination and cognitive control have been reported in AN (Cowdrey et al., 2012; Favaro et al., 2012; Kullmann et al., 2014; Lee et al., 2014), and excessive cognitive control and disorder-related rumination may potentially exacerbate disorder-specific compulsive behaviours. Aberrancies in similar networks have also been reported in other compulsive disorders such as OCD (Beucke et al., 2014; Sridharan, Levitin, & Menon, 2008) and substance dependence (Camchong et al., 2011; Motzkin et al., 2014), and as such dysfunction of these networks could be hypothesised to reflect a neural underpinning for compulsivity across disorders. The final study reported in Chapter 5 aimed to further investigate aberrancies in neural networks at rest in AN (current and past) using a technique called magnetoencephalography (MEG), and to explore the relationship this may have with compulsive self-starvation behaviour measured by the SS developed in Chapter 3.

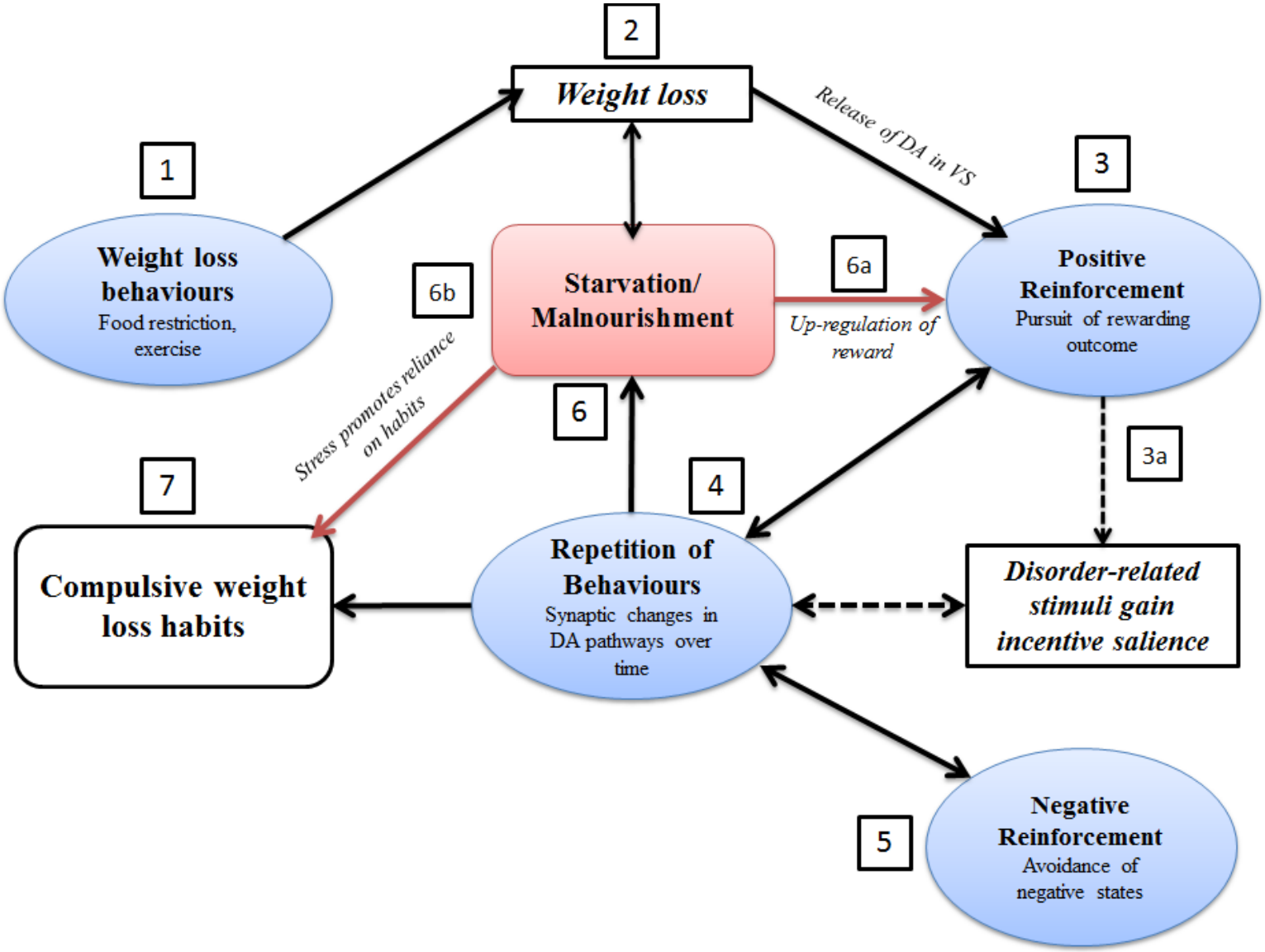
MEG allows the direct measurement of neural activity in the form of magnetic fields elicited by the electrical activity of neurons in the cortex. As such, MEG has a much higher temporal resolution than fMRI, and thus has potential advantages for identifying aberrancies related to the temporal coherence of RSNs. Despite this, Chapter 5 reports no differences in the temporal coherence of RSNs in individuals with current or past AN compared to controls. In light of this, it was not possible to investigate any association with self-reported compulsivity in this study. Methodological limitations related to low statistical power and the limited spatial resolution of MEG may have contributed to the

null result reported in this study. Future studies would benefit from larger sample sizes to combat these limitations.

6.3 A prospective model for the development of compulsive weight-loss behaviours in AN

The results summarised above suggest that whilst parallels with substance dependence can be seen at the level of symptoms and subjective reports in AN (shown in Chapters 2 and 3), this does not appear to be underpinned by a common generalised vulnerability to habit formation during learning (shown in Chapter 4). As suggested in Chapter 4, whilst a generalised vulnerability to habits may not be present in individuals with AN, weight-loss behaviour may still become habitual over time. Aberrantly rewarding dietary restriction and weight-loss in AN, in combination with the physiological consequences of starvation (see Section 1.11), may promote a shift into habitual control of disorder-specific behaviour in AN. In light of the results of the studies reported in this thesis, and the literature reviewed in Chapter 1 (part 2), a potential model is proposed (see Figure 6.1) for the development of compulsive disorder-related habits in AN.

Figure 6.1. Proposed model for the development of compulsive weight loss habits in Anorexia Nervosa (Godier and Park, 2014).



In Figure 6.1 it is suggested that ED-related behaviours, such as food restriction and exercise, begin as goal-directed behaviours aimed at achieving weight-loss (Figure 6.1: 1), and the resulting weight-loss is experienced as rewarding (Figure 6.1: 2). Whilst speculative, this may be positively reinforced by an increase of DA in the VS (Figure 6.1: 3), which plays a crucial role in reinforcing rewarding behaviour (Wise, 2002). An increase in DA in the VS is seen after ingestion of drugs of abuse (Everitt & Robbins, 2005), and increased binding of DA D2/3 receptors in the VS has been reported in individuals recovered from AN (Frank et al., 2005). Positive reinforcement of weight-loss behaviours may result in disorder-related cues gaining incentive salience through conditioned reinforcement (Figure 6.1: 3a), triggering further engagement in weight-loss behaviours (Walsh, 2013). In this way weight-loss behaviour, and the cues associated with this behaviour, may become aberrantly rewarding in AN. This notion is supported by studies showing an increased neural response to disorder-related stimuli in AN in reward-related regions of the brain (Cowdrey et al., 2011; Fladung et al., 2010; Fladung et al., 2013; Giel et al., 2013).

Repetition of aberrantly rewarding weight-loss behaviour over time may also result in synaptic changes in DA pathways, in a similar way to substance dependence (Everitt & Robbins, 2005). Indeed, consistent with this suggestion, changes in the neural response to disorder-related stimuli are seen with increasing duration of AN in the VS, a region which forms part of the mesocorticolimbic DA pathway (Fladung et al., 2010; Fladung et al., 2013). The avoidance of negative states, and the anxiety associated with food, may also become important in negatively reinforcing weight-loss behaviours in the later stages of AN (Selby et al. 2013; Figure 6.1: 5).

Starvation and malnourishment may also further promote weight-loss behaviour in the following ways:

a) Upregulation of reward is observed during starvation (Abrahamsen et al., 1995), and this may lead to disorder-related cues gaining incentive salience (Fladung et al., 2010). It has been suggested that starvation induced reductions in glucose and insulin in AN may lead to an increase in phasic DA transmission in the VS, which binds incentive salience to disorder-related cues (Zink & Weinberger, 2010). Furthermore, AN is associated with increased sensitivity to both reward and punishment, suggesting these individuals have an oversensitive motivational system (Jappe et al., 2011). It is possible that this heightened sensitivity may enhance both positive and negative reinforcement of weight-loss behaviours.

b) Increasing stress has been shown to modulate cognitive memory systems in favour of the neo-striatum dependent habit system in an instrumental learning task (Schwabe et al., 2007). Furthermore, this effect can be mimicked with administration of the stress hormone cortisol (Schwabe, Tegenthoff, Höffken, & Wolf, 2010). This raises the possibility that the stress associated with starvation may promote the compulsive weight-loss behaviours seen in AN. Indeed, currently underweight individuals with AN show increased levels cortisol (Putignano et al., 2001) and even brief food restriction is shown to lead to alterations in gene expression of stress hormones (Guarnieri et al., 2012). Thus in AN, psychological and physical stressors associated with the disorder, as well as chronic food restriction, may promote reliance on habits.

Once weight-loss behaviour has been repeated enough, weight-loss itself may no longer be required as a rewarding outcome for this behaviour to continue, and behaviour may become compulsive and habitual (Walsh, 2013; Figure 6.1: 7). We are unable to conclude anything regarding the neural circuitry associated with compulsive behaviour in AN based on the investigation reported in Chapter 5. However, the dysfunction of regions suggested to be associated with habits previously reported in AN (Rothemund et al., 2011) may reflect the development of disorder-specific habits proposed in this model. This model emphasises the

importance of investigating disorder-specific reward and the effect of starvation in the possible development of habitual weight-loss behaviours in AN.

6.4 Theoretical Implications

The research reported in this thesis was guided by recent suggestion that compulsivity has transdiagnostic significance, upon which disorder-specific themes are superimposed (Robbins et al. 2012; See Section 1.12). The results reported in Chapter 2 provide preliminary evidence that this theory has face validity in relation to compulsive behaviour in AN. Similarities were apparent between the subjective experience of compulsivity in AN, and the DSM-V criteria used to define SUDs, with some individuals describing their behaviour as analogous to an addiction. These parallels were further investigated in Chapter 3, in which the criteria for addiction were adapted to develop new measures of compulsive weight-loss behaviour. The utility of these criteria in capturing compulsive behaviour across disorders, including AN, supports compulsivity as a construct of behaviour with transdiagnostic application. This is also consistent with the NIMH RDoC, which emphasises the need to break away from the use of diagnostic categories for classification, and focus on the variables that define certain dimensions of behaviour, or constructs, seen across psychiatric disorders (Insel et al., 2010).

This approach allows further hypotheses to be generated regarding common behavioural and neurobiological mechanisms that may underlie compulsive behaviour across disorders. One of these hypotheses, investigated in Chapter 4 of this thesis, was derived from Walsh's (2013) habit theory of AN (see Section 1.9), part of which suggests that individuals with AN may have a *generalised* tendency to rely on habits in learning. However, the results reported in Chapter 4 do not support this particular hypothesis, showing that individuals with current and past AN did not differ in their ability to use goal-directed feedback to guide

behaviour in outcome devaluation tasks. This is not however in conflict with the general premise of Walsh's theory that *disorder-specific* behaviour may still become habitual and compulsive over time, as proposed in Figure 6.1. More research is needed to further investigate this proposal. This enquiry would be aided by the development of tasks tapping disorder-specific habits in AN. For example, a recent study by Hildebrandt et al (2015) used a reversal learning paradigm involving visual food stimuli (M&Ms), in which participants were informed they would subsequently receive the food stimuli to increase saliency. Despite previous evidence suggesting only subtle deficits in reversal learning in AN (Sarrar et al., 2011), this study reported that individuals with AN had clear deficits in their ability to extinguish food-cue responses, raising the possibility that deficits are related to the disorder-specific nature of the stimuli (Hildebrandt et al., 2015).

6.5 Clinical Implications

Conceptualising compulsive behaviour as a transdiagnostic concept opens the way for the investigation of treatment strategies aimed at targeting the processes that may underlie compulsive and habitual behaviours across disorders. Whilst Chapter 4 was unable to show a general reliance on habits in AN, as observed in other compulsive disorders, the model proposed in Figure 6.1 suggests disorder-specific habits may develop in AN in the context of the perverse disorder-related reward and starvation. As such it is possible that treatments targeted at the disruption of habitual behaviour may still have potential efficacy in AN. Indeed in Chapter 2, participants with AN emphasised the importance of intervening with potentially compulsive behaviours before they 'solidify' for successful recovery.

Re-patterning habitual behaviours, alongside reversing starvation, has been emphasised as an important component in the treatment of AN (Park et al., 2011, 2012), and some concepts previously aimed at behavioural change and habit breaking in other disorders

have been translated for use in AN. Given the effects of starvation on neurobiological mechanisms that may maintain or exacerbate compulsive behaviour reviewed in Section 1.11, it is likely to be of crucial importance to reverse starvation effects in tandem. Examples of habit breaking strategies are components of Cognitive Remediation Therapy (CRT) and Exposure Response Therapy (ERT). CRT was originally developed for use in the treatment of psychosis, and has also been adapted for use in EDs to improve cognitive flexibility and break cognitive habits. Preliminary research into CRT has found improvements in self-reported cognitive flexibility in individuals with AN (Tchanturia, Davies, & Campbell, 2007). ERT, which targets conditioned fear responses and conditioned reward, has been used in the treatment of OCD (Foa et al., 2005) and addiction (Kaplan, Heinrichs, & Carey, 2011), and some success has been found with graded exposure to food cues in AN, reducing meal-related anxiety and increasing caloric intake post treatment (Steinglass, Albano, et al., 2012; Steinglass et al., 2014).

FMRI findings suggest that brain regions associated with reward processing and habits may be dysfunctional during symptom provocation in AN (Cowdrey et al., 2011; Favaro et al., 2014; Frank et al., 2012; Frank et al., 2013; Rothemund et al., 2011; Uher et al., 2004; Wagner et al., 2007), providing potential neural underpinning for compulsive weight-loss behaviour in AN. Whilst the results of Chapter 5 do not allow us to conclude anything regarding the neural circuitry underpinnings for psychopathology in AN, Chapter 1 outlines the evidence for the dysfunction of neural circuitry suggested to underpin compulsivity across disorders such as AN, OCD and substance dependence. As such, the development of neuromodulatory interventions such as Deep Brain Stimulation (DBS), and the less invasive repetitive transcranial magnetic stimulation (rTMS), may arguably benefit from common neural targets for treatment across disorders. DBS is a reversible, adjustable neurosurgical treatment that involves implanting electrodes that send electrical impulses to chosen locations

in the brain (Rauch, 2003). DBS has been effective in the treatment of OCD when targeting the NAc, and is suggested to normalise excessive fronto-striatal connectivity (Denys et al., 2010; Figee et al., 2013; Kuhn et al., 2007; Liu et al., 2008; Muller et al., 2009). Both animal studies (Henderson et al., 2010; Liu et al., 2008) and DBS in substance-dependent individuals (Kuhn et al., 2007; Muller et al., 2009) have found decreases in addictive behaviours when stimulating the NAc. Given that the NAc area is suggested to be involved in the transition from voluntary to compulsive drug use (Everitt & Robbins, 2005), it is possible that NAc stimulation may disrupt this process and thereby reduce compulsive behaviours. Case reports of DBS to the NAc in AN patients have also reported symptom alleviation both in the presence and absence of comorbid OCD (McLaughlin et al., 2013; Wu, Van Dyck-Lippens, et al., 2013). RTMS, a non-invasive brain stimulation technique often targeting the dlPFC, has been shown to have some efficacy across disorders, reducing cravings and consumption in substance dependence (Barr et al., 2011), decreasing compulsions and obsessions in OCD (Blom, Figee, Vulink, & Denys, 2011; Haghighi et al., 2015), and improving ED psychopathology, anxiety and depression, and potentially the urge to exercise in AN (Khedr, Elfetoh, Ali, & Noamany, 2014; Van den Eynde, Guillaume, Broadbent, Campbell, & Schmidt, 2013).

Novel pharmacological treatments targeting compulsive behaviours might also prove useful in the treatment of compulsivity across disorders. The DA dysfunction seen in many compulsive disorders (See Section 1.8.2) may be a potential target for pharmacological intervention. Given animal and human evidence that DA modulation of glutaminergic transmission plays a role in reward and reinforcement (See Section 1.8.2), glutaminergic medications may also prove useful in compulsive disorders (Kenny & Markou, 2004). The use of drugs that target GABA and glutamate pathways has shown some benefit in the treatment of substance use disorders (Clarke et al., 2004; Olive et al., 2012), binge eating

(Guardia et al., 2011), and OCD (Pittenger et al., 2011), and may also prove beneficial in other disorders in which compulsive behaviour develops.

6.6 General Limitations

Whilst limitations relating to specific studies are outlined in the relevant chapters, more general limitations of this thesis will be discussed in this section.

The research carried out in this thesis was guided by the conceptualisation of compulsivity as transdiagnostic (Robbins et al., 2012), and the NIMH RDoC strategy, which aims to define constructs or dimensions of behaviour that occur on a continuum across diagnostic categories (Cuthbert, 2014). Research approaches to the RDoC are intended to break away from the normal single DSM patient group design, to patients spanning multiple diagnoses, in order to investigate the full range of a certain dimension/behaviour (Insel et al., 2010). For example, to fit the RDoC, a study may include all patients presenting at an anxiety clinic in an investigation of how self-reported fear is related to dysfunction in neural circuitry. Whilst the research reported in this thesis aimed to investigate the construct of compulsivity in AN using different units of measurement (i.e. self-report, behaviour, neural circuitry), only one diagnostic group was used, which is not strictly in line with the RDoC strategy. As such, it is not possible to generalise any results to other ED diagnoses/subtypes, or to individuals with subclinical ED symptoms. However, as research investigating the compulsive nature of behaviour in AN is lacking, this thesis sought to explore the possibility of this construct as a novel avenue for investigation. Future research may benefit from larger samples allowing inclusion of a range of ED diagnoses to further investigate how compulsivity is related to disordered eating.

A second limitation of this thesis was the use of self-report, particularly in Chapters 2 and 3, in which this was the main data collection strategy. There are a number of general

limitations to collecting self-reported data. For example, the researcher is relying on the honesty of participants, their ability to accurately recall information, and their correct interpretation/understanding of the questions asked of them (Fan et al., 2006). This is particularly relevant for Chapters 2 and 3, in which questions were asked online, and as such there was no opportunity for clarification of questions/answers. A further issue with self-report is response bias, in which individuals may show a tendency towards responding in a certain way, regardless of the question (e.g. extreme vs conservative response styles) (Furnham, 1986). There may also be concerns regarding the validity or reliability of the questionnaires used.

In addition to these general self-report limitations, there may be specific issues concerning the use of self-report in an AN sample. Individuals with AN are reported to have poor interoceptive awareness, or uncertainty regarding the somatic or affective state they are experiencing (Merwin, Zucker, Lacy, & Elliott, 2009). In other words there is a discrepancy between the subjective emotional experience of the body, and intellectual cognitions regarding facts about the body in AN (Park et al., 2011), resulting in conflict between the knowledge of being extremely thin, and distressing feeling of fatness in AN (Cooper, Grocutt, Deepak, & Bailey, 2007). This low interoceptive awareness may lead to an inability to accurately self-report their experiences in individuals with AN.

In addition to the self-report questionnaires and questions regarding compulsivity, Chapters 2 and 3, used self-reported diagnosis of AN and scores on the EDE-Q to determine suitability to the study. This raises the question of whether self-reported diagnosis can adequately substitute diagnosis using a clinical interview (such as the SCID and EDE interviews used in Chapters 4 and 5). In the original comparison of the EDE-Q with the EDE interview, Fairburn and Beglin (1994) reported scores on these measures were highly correlated; however there was disagreement in the reporting of binge eating, and on the EDE-

Q Shape Concern subscale. This suggests that some aspects of diagnosis may not be as accurately captured by self-report (Fairburn & Beglin, 1994). Subsequent studies have corroborated these findings, suggesting that whilst there is agreement in behavioural features such as purging and dieting, self-report tends to result in higher scores on more complex features such as binge eating, weight and shape concerns (Wolk, Loeb, & Walsh, 2005). Thus, it may be that clinical interviews are more accurate for certain aspects of diagnosis, such as determining subtypes via assessment of binge-eating. Whilst Chapters 2 and 3 of this thesis relied on self-report, and should be interpreted with caution, capturing the subjective experience of compulsivity in AN may be an important first step in guiding further objective methodologies for investigating this construct. However, whereas Chapter 2 and 3 included both subtypes of AN, Chapters 4 and 5 employed researcher-led diagnostic interviews in the identification of a restrictive-only sample, and as such the problem of subtyping with self-report may have been avoided to an extent.

The isolation of a restrictive sample in Chapters 4 and 5 may also be considered a limitation by some. Whilst Chapters 2 and 3 included both AN subtypes, Chapters 4 and 5 included only those with a current and past diagnosis of *restrictive* AN. As outlined in Section 1.18, both subtypes of AN show high levels of cognitive rigidity, and disorder-related ruminations/obsessions, which may be associated with compulsive nature of the disorder. However, they appear to differ in their levels of impulse control modulation. It was suggested in Section 1.18 that individuals higher in impulsivity may be less able to sustain starvation, instead acting on the body's demand for food, and this may contribute to the emergence of binge-purge behaviours. In contrast, those lower in impulsivity may be better able to maintain restriction, and restrictive behaviours may become more associated with compulsivity alone. For this reason a restrictive sample was used in Chapters 4 and 5, in which sample size restrictions would not allow meaningful comparison of the subtypes. Thus, it is not possible

to generalise the results of these studies beyond the restrictive subtype of AN. For example, the study reported in Chapter 4 suggested that individuals with *restrictive* AN do not show a generalised reliance on habits in two validated outcome-devaluation tasks. However, a previous study has shown a tendency to rely on habits in a learning in individuals with BED (Voon et al., 2014), raising the possibility that binge-eating symptoms may indeed be associated with habit formation. Furthermore, neurobiological differences are also evident between in those with and without binge/purge symptoms, and as such the results of Chapter 5 may again not be generalised beyond the restrictive subtype of AN. Future behavioural and neurobiological research would benefit from the inclusion of both AN subtypes to allow comparison.

6.7 Future Directions for Research

This thesis sought to investigate one particular aspect of AN psychopathology, the compulsive nature of weight-loss behaviours. However, this is just one of many factors likely to contribute to the development and maintenance of the disorder. Whilst specific suggestions for future research have been made in each chapter, this section will outline how future research in general may further our understanding of psychopathology in AN.

The research in this thesis guided by hypotheses generated from the transdiagnostic theory of compulsivity, which suggests that this construct can be seen on a continuum across psychiatric disorders (Robbins et al., 2012). Whilst the data reported in Chapters 2 and 3 suggest this represents an important aspect of behaviour in AN, a number of potentially relevant processes were not investigated in this thesis. For example, reward processing has been shown to be aberrant in AN (Park et al., 2014), and aberrant disorder-related reward may contribute to the development of disorder-specific compulsive behaviour, which persists despite adverse physiological and psychological consequences (Walsh, 2013). In addition,

altered interoceptive processing is reported in AN (Fassino et al., 2004), and may exacerbate the persistence of weight-loss behaviours in AN, as deficits in the perception of bodily states (e.g. hunger) enables restrictive behaviours to continue despite severe malnutrition. Examining these processes and how they relate to compulsive behaviour in AN may help further delineate the mechanisms that lead to the persistence of the disorder.

Whilst the data reported in this thesis has been cross-sectional, longitudinal studies would allow investigation of how weight-loss behaviours become compulsive over time, and potentially contribute to relapse in AN. The model proposed in Section 6.3 suggests that starvation in AN promotes the development of compulsive weight-loss habits in the context of aberrant disorder-related reward. Longitudinal studies would enable researchers to follow the development of compulsive weight-loss behaviours over time, both in relation to aberrant disorder-related reward processing and levels of malnutrition over the course of the disorder. The habit formation theory of AN (Walsh, 2013) suggests that the development of weight-loss habits in AN lead to the persistence of the disorder, and to the high levels of relapse reported in AN. Follow up studies examining the association between the development of compulsive weight-loss behaviour during the course of AN, and relapse rates following treatment, will help to investigate this hypothesis. This will also help determine the importance of developing novel treatment strategies targeting these behaviours to promote lasting recovery.

As emphasised in Section 6.6 it will also be important to investigate the mechanisms underlying compulsive weight-loss behaviour across AN subtypes, in conjunction with larger sample sizes allowing meaningful comparison between these subtypes. An extension to other ED diagnoses, such as BN and BED, will also be useful in determining the relationship between compulsivity and restrictive vs binge/purge ED symptoms, and the mechanisms which may underlie these different aspects of compulsive ED behaviour.

In addition to an extension to other ED subtypes and diagnoses, future research should seek to follow the strategy of the RDoC more closely by conducting large scale investigations of the mechanisms underpinning compulsivity, and how this relates to a variety of psychopathologies. For example, researchers should seek to measure a variety of clinical variables (e.g ED symptoms, obsessive-compulsive symptoms, anxiety), in large samples covering clinical and subclinical populations, and assess the relationship these variables have with behavioural learning mechanisms (e.g. excessive habit formation) and neural circuitry though to be associated with compulsivity. This would allow a more thorough investigation of the behavioural and neural correlates of compulsivity across disorders, and also how these variables are associated with differing symptomology within a single disorder. This will also help to enable the development of novel interventions targeting the behavioural and neural correlates of compulsive behaviour across diagnoses.

6.8 Thesis Conclusions

AN is a psychiatric disorder characterised by relentless self-starvation. It is also associated with high mortality rates, and low rates of recovery. In conjunction with a lack of effective treatments, the serious nature of the disorder emphasises the need for research investigating the underlying processes contributing the persistence of the disorder, and the identification of novel avenues for treatment development. Therefore, this thesis aimed to explore a transdiagnostic perspective of compulsivity in relation to behaviour in AN, in order to help delineate behavioural and neural underpinnings of persistent weight-loss behaviour in AN. The findings of this thesis suggest that compulsivity is an important aspect of behaviour in AN, and may play a role in the persistence of the disorder. Adapting the criteria used to define addiction, provided a useful way in which to measure dietary restriction and exercise behaviours in AN, supporting the utility of taking a transdiagnostic approach towards compulsivity. Whilst this thesis did not find the hypothesised parallels in AN in the investigation of the underlying behavioural and neural mechanisms thought to drive compulsivity in other psychiatric disorders, the findings provide direction for future research investigating the complex processes underpinning weight-loss behaviour in AN. An important question for future research will be to determine how aberrant disorder-related reward and the effects of starvation may contribute to the development of compulsive behaviours in AN. Furthering our understanding of how these complex processes interact in AN may aid the development of effective interventions.

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Health Research Authority

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30 July 2013

Miss Lauren Godier
D.Phil Student
Department of Psychiatry,
University of Oxford.
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OX3 7JX

Dear Miss Godier,

Study title:	**Compulsivity in Anorexia Nervosa: Validation of the Starvation Dependence and Compulsive Exercise Questionnaires in a Clinical Sample**
REC reference:	**13/SC/0370**
IRAS project ID:	**129495**

Thank you for your letter of 23 July 2013 responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Miss Kelly Pullin, nrescommittee.southcentral-berkshireb@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Approved documents

The documents reviewed and approved by the Committee are:

Document	*Version*	*Date*
Advertisement - BEAT advert	1.2	11 July 2009
Advertisement - Poster	1.4	11 July 2013
Covering Letter		11 July 2013
Covering Letter		24 July 2013
Evidence of insurance or indemnity - - Signed Sponsor Letter EC	1306120 LG	20 June 2013

Investigator CV	LG 2013	20 June 2013
Investigator CV	RJP 2013	20 June 2013
Letter from Sponsor -- Signed Sponsor Letter EC	1306120 LG	20 June 2013
Other: Funding Letter		08 June 2013
Other: Starvation Dependence (Non-Validated)	1.3	20 June 2013
Other: Compulsive Exercise (Non-Validated)	1.3	20 June 2013
Other: OxBREAD scale (Non-Validated)	1	20 June 2013
Participant Consent Form: Online Consent Page	1.4	11 July 2013
Participant Information Sheet	1.5	24 July 2013
Protocol	1.2	20 June 2013
Questionnaire: Acceptance and Action Questionnaire (AAQ-2) (Validated)		
Questionnaire: Barratt Impulsiveness Scale (Validated)		
Questionnaire: Clinical _impairment_assessment (CIA) (Validated)		
Questionnaire: Compulsive Exercise Test (CET) (Validated)		
Questionnaire: Eating Disorder Examination Questionnaire (EDE-Q) (Validated)		
Questionnaire: Generalised Anxiety Disorder Assessment GAD-7 (Validated)		
Questionnaire: Leeds Dependence Questionnaire LDQ (Validated)		
Questionnaire: Obsessive-Compulsive Inventory-Revised (OCl-r) (Validated)		
Questionnaire: Yale Food Addiction (YFAS) (Validated)		
Questionnaire: Patient Health Questionnaire (PHQ-9) (Validated)		
REC application	3.5	20 June 2013
Response to Request for Further Information	Letter	11 July 2013
Response to Request for Further Information		24 July 2013

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol • Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

13/SC/0370	**Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours
sincerely
pp.



Dr John B Sheridan
Chair

Email: nrescommittee.southcentral-berkshireb@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Heather House, University of Oxford

UNIVERSITY OF OXFORD
DEPARTMENT OF PSYCHIATRY

WARNEFORD HOSPITAL
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PARTICIPANT INFORMATION SHEET

Compulsivity in Anorexia Nervosa: A Questionnaire Study.

***Chief Investigator**: Lauren Godier (DPhil student), lauren.godier@psych.ox.ac.uk/ 01865 223918*

You are being invited to take part in a research project. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read this information carefully and discuss it with friends, relatives and others if you wish. If there is anything you do not understand, or if you would like more information, please contact the researcher named above. Take time to decide whether you wish to take part. Part 1 of this information sheet will inform you of the purpose of the study and what will happen if you take part. Part 2 gives you more information about the conduct of the study.

Part 1:

What is the purpose of the study?

The purpose of this study is to aid in the development and validation of two new measures of compulsive behaviour in anorexia nervosa. Anorexia nervosa is an eating disorder characterized by extremely low body weight, distorted body image and an obsessive fear of gaining weight. One of the core features of anorexia is the compulsive and driven nature of behaviours such as self starvation and exercise, which are engaged in persistently despite their negative physical and psychological consequences.

There are few standardised measures of compulsivity in eating disorders such as anorexia nervosa. Therefore, this study will aim to help develop and validate new measures of Starvation Dependence and Compulsive Exercise for use in easting disordered populations. We are therefore looking for a sample of individuals who are currently suffering from anorexia nervosa to take part in an online questionnaire study.

What will happen if I take part?

If you agree to take part you will be directed to the questionnaire. You will need to read through the initial information page and tick a box to confirm that you consent to taking part. You will then be able to continue to the questionnaire. The questionnaire will ask you about your eating and exercise habits, as well as your general mood and feelings, and will take approximately 30 minutes to complete.

Expenses and payments

Once you have completed the questionnaires you will be compensated for your time with a £5 Amazon Voucher. This will be sent by email to the email address you provide.

Why have I been chosen?

We are interested in developing and validating the Starvation Dependence and Compulsive Exercise questionnaires in a population of individuals with eating disorders. For that reason we are looking for a sample of individuals who are currently suffering from anorexia nervosa.

You have received information about this study because you have either responded to an advertisement recruiting individuals currently suffering from anorexia nervosa or because you are registered on the Oxford Research List for Anorexia Nervosa (ORLA) and gave us permission to contact you about our research studies.

Exclusion Criteria:

You will not be eligible to take part if you are under the age of 18 or over the age of 65. You will need to be sufficiently fluent in English and not have reading/learning difficulties which will prevent you from fully understanding the study information or questionnaires themselves. You will also not be eligible if you are not **currently** suffering from anorexia nervosa.

Do I have to take part?

No, **taking part is voluntary**. If you don't want to take part, you do not have to give a reason and no pressure will be put on you to try and change your mind. Not taking part in the study or withdrawing from the study will not affect any future health care you may seek. You will not be contacted again after the study unless you give consent for us to do so.

What will happen if I don't want to carry on?

If at any time you feel uncomfortable answering any questions or wish to stop for any reason you will be able to withdraw immediately without penalty. You will not be contacted further, however data collected prior to withdrawal will be kept and may be included in the data analysis.

Will my taking part be confidential?

All the information you give us **will be confidential** and used for the purposes of this study only. The information collected during the study will be used in a way that will not allow you to be identified individually. The data will be collected and stored in accordance with the Data Protection Act 1998. Personal identifiers will be destroyed. Anonymised data will be stored on a password protected computer.

Relevant sections of the records and data collected during the study may be looked at by responsible individuals from the University of Oxford and other regulatory bodies, where it is relevant to your taking part in this research.

What will happen to the study results?

We will make the results available to you, if you wish, and we plan to publish our findings in scientific journals but you will not be identified personally. The results will also form part of the principal investigators doctoral thesis.

The University of Oxford is committed to the dissemination of its research for the benefit of society and the economy and, in support of this commitment, has established an online archive of research materials. This archive includes digital copies of student theses successfully submitted as part of a University of Oxford postgraduate degree programme. Holding the archive online gives easy access for researchers to the full text of freely available theses, thereby increasing the likely impact and use of that research.

If you agree to participate in this project, the research will be written up as a thesis. On successful submission of the thesis, it will deposited both in print and online in the University archives, to facilitate its use in future research. The thesis will be published with embargoed access, meaning there will be a three year period in which public access is restricted. Once this period has lapsed, the thesis will be freely available for public access.

Part 2:
Benefits and risks:

The information we get from this study may help improve our understanding of eating disorders, and help translate findings into novel treatments, which are desperately needed. Having validated measures of compulsivity that are specific for eating disorders will help detect these behaviours not only in individuals currently suffering from an eating disorder, but also in those who may be vulnerable to developing an eating disorder such as anorexia nervosa.

There are no risks involved in taking part in this questionnaire study. However, if at any time you feel uncomfortable answering any questions, or wish to withdraw from the study, you are able to do so without penalty.

What if there is a problem?

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact *(Lauren Godier: 01865223918, lauren.godier@psych.ox.ac.uk)* or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224 or the head of CTRG, email ctrg@admin.ox.ac.uk .

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London, policy numbered :WD1200463)

Who has reviewed this study?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee, to protect your interests. This study has been reviewed by ….

Funding:
This work is funded by the Medical Research Council (MRC).

What do I do now?

Think about the information on this sheet, and contact the principal researcher if you are not sure about anything, have any further questions regarding the study, or would like any further information before you decide to take part. If you would like to take part, you will be provided the link to the questionnaire. The first page will require to you to give your consent to take part in the study by ticking a box. Once you have given consent, you will be able to go on and complete the questionnaire.

For further information:
Lauren Godier (Chief Investigator)
Department of Psychiatry
Warneford Hospital,
Oxford,
OX3 7DX
lauren.godier@psych.ox.ac.uk
01865 223918 (office hours only)

You can also seek independent general advice from the research information website 'Involve' – http://www.invo.org.uk/

THANK YOU FOR TAKING TIME TO READ THIS INFORMATION SHEET

Thank you for deciding to take part in this questionnaire.

Please read the information below and tick the box to confirm you would like to take part. You will not be able to continue and complete the questionnaire unless the box is ticked.

The following questionnaire will ask you a number of questions regarding your eating and exercise habits, and well as your general mood and feelings. This should take you approximately 30 minutes to complete.

Please answer every question to the best of your knowledge. If you are unsure about how to answer any questions, please click the 'more info' link next to the question for more information.

Please complete the questionnaire in one session, once you have exited the questionnaire you will be unable to go back and finish it.

By ticking the box below you confirm the following:

1. You have read and understood the participant information sheet sent to you via email by the principal investigator.
2. You have asked any questions you may have via email to the principal investigator, and these have been answered satisfactorily.
3. You understand you are under no obligation to complete any questions you do not feel comfortable completing.
4. You understand you are free to withdraw from the study at any time without giving a reason and without penalty.
5. You understand what will happen to the personal data you have provided, how this data will be stored and disposed of.
6. You understand that this research will form part of the principal investigators doctoral thesis ad what this means for the publication and storage of your data.
7. You understand this project has been reviewed by…
8. You understand the complaints and concerns procedure.

Please tick the box if you agree to take part.☐

EATING DISORDER EXAMINATION QUESTIONNAIRE

Instructions: The following questions are concerned with the past four weeks (28 days) only. Please read each question carefully. Please answer all of the questions. Please only choose one answer for each question. Thank you.

Questions 1 to 12: Please circle the appropriate number on the right. Remember that the questions only refer to the past four weeks (28 days) only.

On how many of the past 28 days ……	No days	1-5 days	6-12 days	13-15 days	16-22 days	23-27 days	Every day
1Have you been deliberately trying to limit the amount of food you eat to influence your shape or weight (whether or not you have succeeded)?	0	1	2	3	4	5	6
2Have you gone for long periods of time (8 waking hours or more) without eating anything at all in order to influence your shape or weight?	0	1	2	3	4	5	6
3Have you tried to exclude from your diet any foods that you like in order to influence your shape or weight (whether or not you have succeeded)?	0	1	2	3	4	5	6
4Have you tried to follow definite rules regarding your eating (for example, a calorie limit) in order to influence your shape or weight (whether or not you have succeeded)?	0	1	2	3	4	5	6
5Have you had a definite desire to have an empty stomach with the aim of influencing your shape or weight?	0	1	2	3	4	5	6
6Have you had a definite desire to have a totally flat stomach?	0	1	2	3	4	5	6
7Has thinking about food, eating or calories made it very difficult to concentrate on things you are interested in (for example, working, following a conversation, or reading)?	0	1	2	3	4	5	6
8Has thinking about shape or weight made it very difficult to concentrate on things you are interested in (for example, working, following a conversation, or reading)?	0	1	2	3	4	5	6
9Have you had a definite fear of losing control over eating?	0	1	2	3	4	5	6
10Have you had a definite fear that you might gain weight?	0	1	2	3	4	5	6
11Have you felt fat?	0	1	2	3	4	5	6
12Have you had a strong desire to lose weight?	0	1	2	3	4	5	6

Questions 13-18: Please fill in the appropriate number in the boxes on the right. Remember that the questions only refer to the past four weeks (28 days).

Over the past four weeks (28 days)…….

13	Over the past 28 days, how many <u>times</u> have you eaten what other people would regard as an <u>unusually large amount of food</u> (given the circumstances)?	……..
1.	….On how many of these times did you have a sense of having lost control over your eating (at the time that you were eating)?	……..
•	Over the past 28 days, on how many **<u>DAYS</u>** have such episodes of overeating occurred (i.e. you have eaten an unusually large amount of food and have had a sense of loss of control at the time)?	……..
•	Over the past 28 days, how many <u>times</u> have you made yourself sick (vomit) as a means of controlling your shape or weight?	……..
•	Over the past 28 days, how many <u>times</u> have you taken laxatives as a means of controlling your shape or weight?	……..
18	Over the past 28 days, how many <u>times</u> have you exercised in a "driven" or "compulsive" way as a means of controlling your weight, shape or amount of fat or to burn off calories?	……..

Questions 19-21: Please circle the appropriate number. <u>Please note that for these questions the term "binge eating" means</u> eating what others would regard as an unusually large amount of food for the circumstances, accompanied by a sense of having lost control over eating.

• Over the past 28 days, on how many days have you eaten in secret (ie, furtively)?.....Do not count episodes of binge eating	No days	1-5 days	6-12 days	13-15 days	16-22 days	23-27 days	Every day
	0	1	2	3	4	5	6

• On what proportion of the times that you have eaten have you felt guilty (felt that you've done wrong) because of its effect on your shape or weight? .....Do not count episodes of binge eating	None of the times	A few of the times	Less than half	Half of the times	More than half	Most of the time	Every time
	0	1	2	3	4	5	6

• Over the past 28 days, how concerned have you been about other people seeing you eat? .....Do not count episodes of binge eating	Not at all		Slightly	Moderately			Markedly
	0	1	2	3	4	5	6

Questions 22-28: Please circle the appropriate number on the right. Remember that the questions only refer to the past four weeks (28 days)

On how many of the past 28 days ……	Not at all		Slightly		Moderately		Markedly
22 Has your weight influenced how you think about (judge) yourself as a person?	0	1	2	3	4	5	6
23 Has your shape influenced how you think about (judge) yourself as a person?	0	1	2	3	4	5	6
24 How much would it have upset you if you had been asked to weigh yourself once a week (no more, or less, often) for the next four weeks?	0	1	2	3	4	5	6
25 How dissatisfied have you been with your weight?	0	1	2	3	4	5	6
26 How dissatisfied have you been with your shape?	0	1	2	3	4	5	6
27 How uncomfortable have you felt seeing your body (for example, seeing your shape in the mirror, in a shop window reflection, while undressing or taking a bath or shower)?	0	1	2	3	4	5	6
28 How uncomfortable have you felt about others seeing your shape or figure (for example, in communal changing rooms, when swimming, or wearing tight clothes)?	0	1	2	3	4	5	6

What is your weight at present? (Please give your best estimate). …….

What is your height? (Please give your best estimate).

…… ….

If female: Over the past three-to-four months have you missed any menstrual periods? ……

If so, how many…….

Have you been taking the "pill"? ……..

THANK YOU

EDE-Q reproduced with permission. Fairburn and Beglin (2008). In Fairburn, C. G. (2008). *Cognitive Behavior Therapy and Eating Disorders.* Guilford Press, New York.

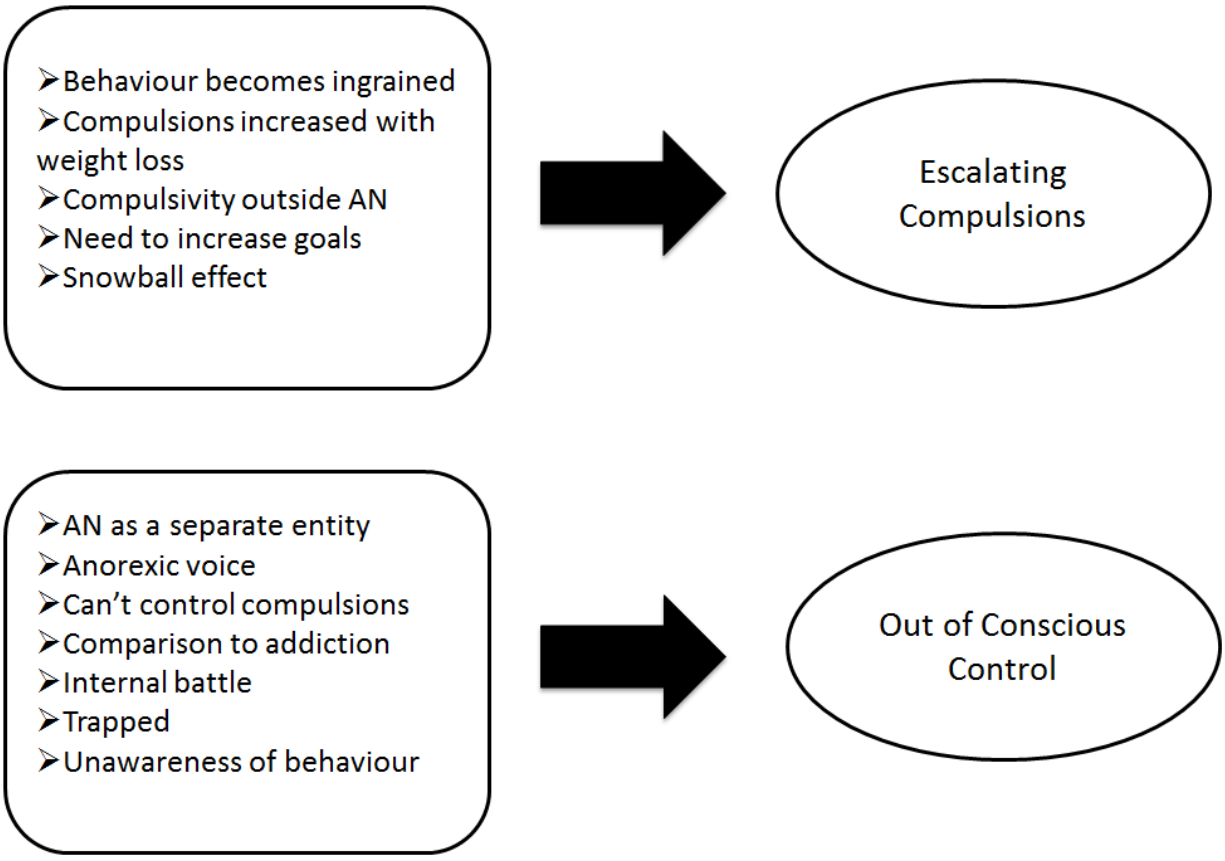
Clinical Impairment Assessment (Bohn & Fairburn, 2008)

INSTRUCTIONS

Please place an 'X' in the column which best describes how your eating habits, exercising or feelings about your eating, shape or weight have affected your life over the past four weeks (28 days). Thank you.

	Over the past 28 days, to what extent have your …eating habits …exercising or feelings about your eating, shape or weight …	Not at all	A little	Quite a bit	A lot
1	… made it difficult to concentrate?				
2	… made you feel critical of yourself?				
3	… stopped you going out with others?				
4	… affected your work performance (if applicable)?				
5	… made you forgetful?				
6	… affected your ability to make everyday decisions?				
7	… interfered with meals with family or friends?				
8	… made you upset?				
9	… made you feel ashamed of yourself?				
10	… made it difficult to eat out with others?				
11	… made you feel guilty?				
12	… interfered with you doing things you used to enjoy?				
13	… made you absent-minded?				
14	… made you feel a failure?				
15	… interfered with your relationships with others?				
16	… made you worry?				

Example of refining themes



Final Coding Scheme

Theme	Sub-Themes	Code definition
1. Compulsivity is central to AN		Text coded if describes compulsive nature of behaviour as a characteristic behaviour in AN, playing a central role in development and/or maintenance of behaviour in the disorder.
2. Impaired control	*2.1 Out of conscious control*	Text coded if describes inability to control the need to carry out weight loss related behaviour, and/or behaviour feels to be driven by something external to the self.
	2.2 Go out of their way to perform behaviour	Text coded if describes the need to overcome all obstacles to carry out weight loss related behaviour.
	2. 3 Desire/attempts to stop	Text coded if describes wanting to cease weight loss related behaviour, or reports unsuccessful attempts to cease weight loss related behaviour despite wanting to.
3. Functional Impairment	*3.1 Time consumed by compulsions*	Text coded if describes much time being consumed by compulsions and/or obsessions, or describes weight loss related behaviour as taking over time previously spent on other activities.
	3.2 Interpersonal and occupational impairment	Text coded if described worsening interpersonal relationships (e.g. with friends and family), and/or an inability to fulfil occupational commitments and attend occupational/social events due to the need to carry out weight loss related behaviours.

4. Detrimental Use	*4. 1 Continued behaviour despite insight*	Text coded if describes continuation of weight loss behaviours whilst acknowledging the link between behaviour and negative psychological and physical consequences.
	4.2 Behaviour causes psychological distress	Text coded if describe acknowledgement of a direct link between presence of compulsive behaviours with psychological distress and/or a negative emotional state. Refer to codes 6 and 7 if describes negative emotions as a trigger for behaviour, or reaction to being prevented from behaviour.
5. Escalating Compulsions		Text coded if describes compulsions increasing over time (i.e. increasing rules/targets/calories limits), increasing in parallel with weight loss, and/or compulsions spreading to other aspects of life.
6. Negative Reactions when attempts are made to prevent compulsions	*6.1 Negative feelings*	Text coded if describe experiencing negative emotions in reaction to be prevented or being unable to carry out weight loss related behaviours.
	6.2 Physical feelings	Text coded if describes experiencing a physical reaction to being prevented or being unable to carry out weight loss related behaviours.
	6.3 Swapping one compulsion for another	Text coded if describe feeling the need to replace one behaviour with another in order to relieve negative feelings associated with being prevented or being unable to carry out weight loss related behaviours.
7. Emotional triggers	*7.1 Negative feelings*	Text coded if describes a negative emotional state as preceding engagement in weight loss related behaviours.
	7.2 Positive feelings	Text coded if describes the pursuit of a positive emotion as the motivation for carry out weight loss related behaviours.

8. Role in Recovery	*8.1 Compulsivity as a barrier to recovery*	Text coded if described the compulsive nature of behaviour as preventing/delaying recovery and/or making recovery particularly difficult. Also code if describe as an important target for recovery.
	8.2 Strategies to reduce compulsions	Text coded if describes strategies/contexts in which compulsions may be reduced/eased.

MEDICAL SCIENCES INTER DIVISIONAL RESEARCH ETHICS COMMITTEE
Medical Sciences Divisional Office

University of Oxford, Level 3, John Radcliffe Hospital, Headington, Oxford, OX3 9DU
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ethics@medsci.ox.ac.uk http://www.medsci.ox.ac.uk

CONFIDENTIAL Ref: **MSD-IDREC-C1-2013-039**

Ms Lauren Godier
University Department of Psychiatry
Warneford Hospital
Oxford
OX3 7JX

28th February 2013

Dear Ms Godier

I am writing to acknowledge receipt of your CUREC/1 form for your project: **Compulsivity in Anorexia Nervosa: Development and validation of two new measures.**

On the basis of the information you have provided this has now been approved by the Medical Sciences IDREC **subject to:**

a) your following the BPS guidelines for online research;

b) it is your responsibility to comply with the requirements for administering any tests or questionnaires and if in doubt to contact the publisher of those tests or questionnaires.

The reference number for this project is **MSD-IDREC-C1-2013-039** and may I remind you that your project may be reviewed at some stage during an annual audit of projects.

Amendments

Should you at some stage alter some of the techniques or procedures then you should first undertake a checklist (CUREC/1) to see whether these changes alter the ethics of the research. If these remain the same then the committee will require notification of the changes to lodge with the project. If they do not remain the same then you may need to complete a CUREC/2 form and undergo further scrutiny by the committee.

Please do not hesitate to contact me if you have any queries about this.

Yours sincerely

Rosie Mortimer
Senior Assistant Registrar & Secretary to IDREC

WARNEFORD HOSPITAL

OXFORD

OX3 7JX

UNIVERSITY OF OXFORD

DEPARTMENT OF PSYCHIATRY

PARTICIPANT INFORMATION SHEET

Research title: Compulsivity in eating and exercise behaviours.

***Principal Researcher**: Lauren Godier (DPhil student), lauren.godier@psych.ox.ac.uk, 01865223918*

Many individuals engage in dieting and exercise as part of a healthy lifestyle. However, for some people these behaviours become maladaptive and may feel out of control. Those who are involved in sports teams, or who have suffered from an eating disorder, represent populations who, for different reasons may been exposed to extreme exercise and dietary regimes. We are interested in looking at the element of compulsivity in eating and exercise behaviours in these risk groups and how this may relate to eating disorder symptoms. In order to further investigate this we are looking for individuals involved in sports teams, individuals who have a history of the eating disorder anorexia nervosa, and healthy individuals not involved in sports, to take part in an online questionnaire study.

What will I have to do if I take part?

If you agree to take part, you will be asked to complete an online questionnaire. There are no right or wrong answers. The questionnaires will take approximately 20-25 minutes in total. Please note that you may feel that some of the questions are not directly applicable to you. Please do your best to answer all the questions. At a later date you may be contacted again and asked to complete another set of questionnaires, although this is optional. You will receive a £5 Amazon Voucher on completion of the first set of questionnaires, and on completion of the second set if you are contacted again.

Do I have to take part?

No, **taking part is voluntary**. If you don't want to take part, you do not have to give a reason and no pressure will be put on you to try and change your mind. There will be no penalty if you decide to withdraw your participation from the study. You will not be contacted again after the study is completed unless you give consent for us to do so.

If I agree to take part what happens to what I say?

All the information you give us **will be confidential** and used for the purposes of this study only. The data collected will be accessed by the principal researcher and authorised individuals only. The information collected during the study will be used in a way that will not allow you to be identified individually. The data will be collected and stored in accordance with the Data Protection Act 1998. Personal identifiers will be destroyed. Anonymised data will be stored on a password protected computer and any paper records will be stored in a locked filing cabinet.

What will happen to the study results?

We will make the results available to you, if you wish, and we plan to publish our findings in scientific journals but you will not be identified personally. The results will also form part of the principal investigators doctoral thesis.

The University of Oxford is committed to the dissemination of its research for the benefit of society and the economy and, in support of this commitment, has established an online archive of research

materials. This archive includes digital copies of student theses successfully submitted as part of a University of Oxford postgraduate degree programme. Holding the archive online gives easy access for researchers to the full text of freely available theses, thereby increasing the likely impact and use of that research.

If you agree to participate in this project, the research will be written up as a thesis. On successful submission of the thesis, it will deposited both in print and online in the University archives, to facilitate its use in future research. The thesis will be published with embargoed access, meaning there will be a three year period in which public access is restricted. Once this period has lapsed, the thesis will be freely available for public access.

What are the benefits and risks of taking part?

The information we get from this study may help improve our understanding of eating disorders, and help translate findings into novel treatments, which are desperately needed.

There are no risks involved in taking part in this questionnaire study. However, if at any time you feel uncomfortable answering any questions, or wish to withdraw from the study, you are able to do so without penalty. In recognition of your time and help you will receive a £5 Amazon voucher for each set of questionnaires you complete.

What do I do now?

Think about the information on this sheet, and contact the principal researcher if you are not sure about anything, have any further questions regarding the study, or would like any further information before you decide to take part. If you agree to take part, follow the web link on this page which will lead you to an electronic consent form. The consent form will not be used to identify you. It will be filed separately from all other information. Once you have given consent, you will be directed to the questionnaire.

If you are interested in participating in this study, please follow this link to access the consent form:

https://docs.google.com/file/d/0B08bvRPjqwuCNWxQajVIRHNDNDg/edit?usp=sharing

THIS PROJECT HAS BEEN REVIEWED BY, AND RECEIVED ETHICAL CLEARANCE FROM, THE UNIVERSITY OF OXFORD RESEARCH ETHICS COMMITTEE

If you have a concern about any aspect of this project, please speak to the researcher concerned (lauren.godier@psych.ox.ac.uk, 01865223918) who will do her best to answer your query. If you remain unhappy and wish to make a formal complaint, please contact the Research Ethics Committee at the University of Oxford (ethics@medsci.ox.ac.uk; Medical Sciences Inter-Divisional Research Ethics Committee, Medical Sciences Divisional Office, Level 3 John Radcliffe Hospital,Oxford, OX3 9DU , UK).

WARNEFORD HOSPITAL

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OX3 7JX

UNIVERSITY OF OXFORD

DEPARTMENT OF PSYCHIATRY

CONSENT FORM

Compulsivity in eating and exercise behaviours.

***Principal Researcher**: Lauren Godier (DPhil student), lauren.godier@psych.ox.ac.uk, 01865223918*

Many individuals engage in dieting and exercise as part of a healthy lifestyle. However, for some people these behaviours become maladaptive and may feel out of control. Those who are involved in sports teams represent a population who are exposed to high levels of exercise and may be required to undertake certain diets. For this reason, we are interested in looking at the eating and exercise behaviours within this group and how they may relate to eating disorder symptoms. In order to look at this we are looking for individuals involved in sports teams, individuals who have experience of an eating disorder, and healthy individuals not involved in sports to take part in an online questionnaire study. **Please read carefully through and complete the following questions.**

Have you read and understood the participant information sheet?
YES/NO

Have you had the opportunity to ask questions and discuss the study? YES/NO

Have all your questions been asked satisfactorily? YES/NO

Do you understand that you are free to withdraw from the study without penalty:

At any time YES/NO YES/NO

Without giving any reason YES/NO

Do you understand what will happen to the personal data you have provided, how this data will be stored and disposed of?

YES/NO

Do you understand that this research will form part of the principal investigators doctoral thesis and what this means for the publication and storage of your data?

YES/NO

Do you understand that this project has been reviewed by the University of Oxford Central University Research Ethics Committee and has received ethical clearance? YES/NO

Do you understand the complaints and concerns procedure? YES/NO

The study has been explained to my satisfaction and I understand that I am free to ask any questions or to withdraw at any time. I agree to take part.

Signature of the participant:…….. Date:……..

Name (in block capitals):……..

I have explained the research to the above participant and he/she has agreed to take part

Signature of the researcher:…….. Date……..

Name (in block capitals)…….

UNIVERSITY OF OXFORD
DEPARTMENT OF PSYCHIATRY

WARNEFORD HOSPITAL
OXFORD
OX3 7JX

PARTICIPANT INFORMATION SHEET

Compulsivity in Anorexia Nervosa: A Questionnaire Study.

***Chief Investigator**: Lauren Godier (DPhil student), lauren.godier@psych.ox.ac.uk/ 01865 223918*

You are being invited to take part in a research project. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read this information carefully and discuss it with friends, relatives and others if you wish. If there is anything you do not understand, or if you would like more information, please contact the researcher named above. Take time to decide whether you wish to take part. Part 1 of this information sheet will inform you of the purpose of the study and what will happen if you take part. Part 2 gives you more information about the conduct of the study.

Part 1:

What is the purpose of the study?

The purpose of this study is to aid in the development and validation of two new measures of compulsive behaviour in anorexia nervosa. Anorexia nervosa is an eating disorder characterized by extremely low body weight, distorted body image and an obsessive fear of gaining weight. One of the core features of anorexia is the compulsive and driven nature of behaviours such as self starvation and exercise, which are engaged in persistently despite their negative physical and psychological consequences.

There are few standardised measures of compulsivity in eating disorders such as anorexia nervosa. Therefore, this study will aim to help develop and validate new measures of Starvation Dependence and Compulsive Exercise for use in easting disordered populations. We are therefore looking for a sample of individuals who are currently suffering from anorexia nervosa to take part in an online questionnaire study.

This research study will form part of the Chief Investigators PhD thesis.

What will happen if I take part?

If you agree to take part you will be directed to the questionnaire. You will need to read through the initial information page and tick a box to confirm that you consent to taking part. You will then be able to continue to the questionnaire. The questionnaire will ask you about your eating and exercise habits, as well as your general mood and feelings, and will take approximately 30 minutes to complete.

Expenses and payments

Once you have completed the questionnaires you will be compensated for your time with a £5 Amazon Voucher. This will be sent by email to the email address you provide.

Why have I been chosen?

We are interested in developing and validating the Starvation Dependence and Compulsive Exercise questionnaires in a population of individuals with eating disorders. For that reason we are looking for a sample of individuals who are currently suffering from anorexia nervosa.

You have received information about this study because you have either responded to an advertisement recruiting individuals currently suffering from anorexia nervosa or because you are registered on the Oxford Research List for Anorexia Nervosa (ORLA) and gave us permission to contact you about our research studies.

Exclusion Criteria:

You will not be eligible to take part if you are under the age of 18 or over the age of 65. You will need to be sufficiently fluent in English and not have reading/learning difficulties which will prevent you from fully understanding the study information or questionnaires themselves. You will also not be eligible if you are not **currently** suffering from anorexia nervosa.

Do I have to take part?

No, **taking part is voluntary**. If you don't want to take part, you do not have to give a reason and no pressure will be put on you to try and change your mind. Not taking part in the study or withdrawing from the study will not affect any future health care you may seek. You will not be contacted again after the study unless you give consent for us to do so.

What will happen if I don't want to carry on?

If at any time you feel uncomfortable answering any questions or wish to stop for any reason you will be able to withdraw immediately without penalty. You will not be contacted further, however data collected prior to withdrawal will be kept and may be included in the data analysis.

Will my taking part be confidential?

All the information you give us **will be confidential** and used for the purposes of this study only. The information collected during the study will be used in a way that will not allow you to be identified individually. The data will be collected and stored in accordance with the Data Protection Act 1998. Personal identifiers will be destroyed. Anonymised data will be stored on a password protected computer.

Relevant sections of the records and data collected during the study may be looked at by responsible individuals from the University of Oxford and other regulatory bodies, where it is relevant to your taking part in this research.

What will happen to the study results?

We will make the results available to you, if you wish, and we plan to publish our findings in scientific journals but you will not be identified personally. The results will also form part of the chief investigators PhD thesis.

The University of Oxford is committed to the dissemination of its research for the benefit of society and the economy and, in support of this commitment, has established an online archive of research materials. This archive includes digital copies of student theses successfully submitted as part of a University of Oxford postgraduate degree programme. Holding the archive

online gives easy access for researchers to the full text of freely available theses, thereby increasing the likely impact and use of that research.

If you agree to participate in this project, the research will be written up as a thesis. On successful submission of the thesis, it will deposited both in print and online in the University archives, to facilitate its use in future research. The thesis will be published with embargoed access, meaning there will be a three year period in which public access is restricted. Once this period has lapsed, the thesis will be freely available for public access.

Part 2:
What are the possible benefits of taking part?

The information we get from this study may help improve our understanding of eating disorders, and help translate findings into novel treatments, which are desperately needed. Having validated measures of compulsivity that are specific for eating disorders will help detect these behaviours not only in individuals currently suffering from an eating disorder, but also in those who may be vulnerable to developing an eating disorder such as anorexia nervosa.

What are the possible disadvantages of participation?

Participation in this study will require you to answer questions which are sensitive in nature, such as those relating to eating disorders and other psychological issues. These questions may cause some emotional distress or raise concerns for some individuals.

If during the study you experience any distress or feel uncomfortable answering these questions, or wish to withdraw from the study for any reason, you are able to stop at any time without penalty. If the issues raised in this study cause you concern regarding your own well being, we would advise that you contact your GP or your service provider if you are currently under eating disorder services. If you feel that you require specialist advice you can contact Dr Rebecca Park (oxbread@psych.ox.ac.uk/ 01865223918) who is a consultant psychiatrist in eating disorders.

What if there is a problem?

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact *(Lauren Godier: 01865223918, lauren.godier@psych.ox.ac.uk)* or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224 or the head of CTRG, email ctrg@admin.ox.ac.uk .

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London, policy numbered :WD1200463)

Who has reviewed this study?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee, to protect your interests. This study has been reviewed by the Proportionate Review Sub-Committee of the NRES Committee South Central – Berkshire B (Ref: 13/SC/0370).

Funding:
This work will form part of the Chief Investigators PhD thesis and is funded by the Medical Research Council (MRC).

What do I do now?

Think about the information on this sheet, and contact the chief investigator if you are not sure about anything, have any further questions regarding the study, or would like any further information before you decide to take part. If you would like to take part, you will be provided the link to the questionnaire. The first page will require to you to give your consent to take part in the study by ticking a box. Once you have given consent, you will be able to go on and complete the questionnaire.

For further information:

Lauren Godier (Chief Investigator)
Department of Psychiatry
Warneford Hospital,
Oxford,
OX3 7DX
lauren.godier@psych.ox.ac.uk
01865 223918 (office hours only)

You can also seek independent general advice from the research information website 'Involve' – http://www.invo.org.uk/

THANK YOU FOR TAKING TIME TO READ THIS INFORMATION SHEET

Thank you for deciding to take part in this questionnaire.

Please read the information below and tick the box to confirm you would like to take part. You will not be able to continue and complete the questionnaire unless the box is ticked.

The following questionnaire will ask you a number of questions regarding your eating and exercise habits, and well as your general mood and feelings. This should take you approximately 30 minutes to complete.

Please answer every question to the best of your knowledge. If you are unsure about how to answer any questions, please click the 'more info' link next to the question for more information.

Please complete the questionnaire in one session, once you have exited the questionnaire you will be unable to go back and finish it.

By ticking the box below you confirm the following:

1. You have read and understood the participant information sheet sent to you via email by the principal investigator.
2. You have asked any questions you may have via email to the principal investigator, and these have been answered satisfactorily.
3. You understand you are under no obligation to complete any questions you do not feel comfortable completing.
4. You understand you are free to withdraw from the study at any time without giving a reason and without penalty.
5. You understand what will happen to the personal data you have provided, how this data will be stored and disposed of.
6. You understand that this research will form part of the principal investigators doctoral thesis ad what this means for the publication and storage of your data.
7. You understand this project has been reviewed by…
8. You understand the complaints and concerns procedure.

Please tick the box if you agree to take part. ☐

The Self-Starvation Scale

The survey asks you about you eating habits in the past four weeks. People sometimes feel they have to restrict their food intake, or the intake of specific foods.

When answering the following questions please think about any foods you have restricted in the past four weeks.

IN THE PAST 4 WEEKS	No days	1-5 days	6-12 days	13-15 days	16-22 days	23-27 days	Every day
1. I find that when I start restricting my food intake, I end up restricting much more than I planned.	0	1	2	3	4	5	6
2. I find myself continuing to restrict my food intake, even though I am hungry.	0	1	2	3	4	5	6
3. I restrict my food intake to the point where I feel physically ill.	0	1	2	3	4	5	6
4. Not restricting my food intake or having to eat more food is something I worry about.	0	1	2	3	4	5	6
5. I spend a lot of time feeling sluggish or fatigued from restricting my food intake.	0	1	2	3	4	5	6
6. I find myself constantly restricting my food intake throughout the day.	0	1	2	3	4	5	6
7. I find that when I am unable to restrict my food intake, I will go out of my way to find a way to do so.	0	1	2	3	4	5	6
8. I have restricted my food intake so much that I have concentrated on this instead of working, spending time with family and friends, or doing other activities I enjoy.	0	1	2	3	4	5	6
9. I have restricted my food intake so much that I have spent time dealing with negative feelings from restricting instead of working, spending time with family and friends, or doing other activities I enjoy.	0	1	2	3	4	5	6
10. There have been times when I have avoided professional or social situations involving food because I was afraid I would have to restrict my food intake.	0	1	2	3	4	5	6
11. There have been times when I have avoided professional or social situations involving food because I felt I would be unable to restrict certain foods.	0	1	2	3	4	5	6
12. I have had withdrawal symptoms such as agitation, anxiety, or other physical symptoms when I have been unable to restrict my food intake.	0	1	2	3	4	5	6
13. I have restricted my food intake to prevent feelings of anxiety, agitation, or other physical symptoms that were developing.	0	1	2	3	4	5	6
14. I have found that I have an elevated desire or urges to restrict my food intake.	0	1	2	3	4	5	6
15. My behaviour with respect to restricting my food intake causes significant distress.	0	1	2	3	4	5	6
16. I experience significant problems in my ability to function effectively (daily routine, job/school, social activities, family activities, health difficulties) because of restricting my food intake.	0	1	2	3	4	5	6

The Compulsive Exercise Scale

The survey asks you about you exercise habits in the past four weeks. People sometimes have difficulty controlling the amount of exercise they do.

When answering the following questions, think about the different types of exercise you engage in and times in which you have felt unable to control the amount of exercise you do.

IN THE PAST 4 WEEKS	No days	1-5 days	6-12 days	13-15 days	16-22 days	23-27 days	Every day
1. I find that when I start to exercise, I end up exercising more than I planned.	0	1	2	3	4	5	6
2. I find myself continuing to exercise, even when I am too tired to do so.	0	1	2	3	4	5	6
3. I exercise to the point where I feel physically ill.	0	1	2	3	4	5	6
4. Not being able to exercise is something I worry about.	0	1	2	3	4	5	6
5. I spend a lot of time feeling sluggish or fatigued from exercise.	0	1	2	3	4	5	6
6. I find myself constantly trying to exercise throughout the day.	0	1	2	3	4	5	6
7. I find that when I am unable to exercise, I will go out of my way to find a way to do so.	0	1	2	3	4	5	6
8. I have focused on exercise so much that I have concentrated on this instead of doing other activities.	0	1	2	3	4	5	6
9. I have spent time dealing with negative feelings from exercising instead of doing other activities e.g. working, spending time with family or friends.	0	1	2	3	4	5	6
10. I have avoided professional or social situations because I would not be able to exercise.	0	1	2	3	4	5	6
11. I have had withdrawal symptoms such as agitation, anxiety, or other physical symptoms when I have been unable to exercise.	0	1	2	3	4	5	6
12. I have exercised to prevent feelings of anxiety, agitation, or other physical symptoms that were developing.	0	1	2	3	4	5	6
13. I have found that I have an elevated desire or urges to exercise.	0	1	2	3	4	5	6
14. My behaviour with respect to exercising causes significant distress.	0	1	2	3	4	5	6
15. I experience significant problems in my ability to function (job/school, social or family activities) because of exercise.	0	1	2	3	4	5	6

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
☐	☐	☐	☐

GAD-7

Identifier | Date

Please read each statement and record a number 0, 1, 2 or 3 which indicates how much the statement applied to you over the past two weeks. There are no right or wrong answers. Do not spend too much time on any one statement. This assessment is not intended to be a diagnosis. If you are concerned about your results in any way, please speak with a qualified health professional.

0 = Not at all 1 = Several days 2 = More than half the days 3 = Nearly every day

1	Feeling nervous, anxious or on edge	
2	Not being able to stop or control worrying	
3	Worrying too much about different things	
4	Trouble relaxing	
5	Being so restless that it is hard to sit still	
6	Becoming easily annoyed or irritable	
7	Feeling afraid as if something awful might happen	

Total GAD-7 score =

AAQ-II, Bond et al. 2010.

Please rate how true each statement is for you by writing the number next to it.

1 Never true
2 Very seldom true
3 Seldom true
4 Sometimes true
5 Frequently true
6 Almost always true
7 Always true

It's ok if I remember something unpleasant.

My painful experiences and memories make it difficult to live a life that i would value

I am afraid of my feelings

I worry about not being able to control my worries and feelings.

My painful memories prevent me from having a fulfilling life.

I am in control of my life.

Emotions cause problems in my life.

It seems that most people are handling their lives better than i am.

My worries get in the way of my success.

My thoughts and feelings do not get in the way of how i want to live my life.

Yale Food Addiction Scale (Gearhardt, Corbin, Brownell, 2009)

This survey asks about your eating habits in the past year. People sometimes have difficulty controlling their intake of certain foods such as:

8 Sweets like ice cream, chocolate, doughnuts, cookies, cake, candy, ice cream
9 Starches like white bread, rolls, pasta, and rice
10 Salty snacks like chips, pretzels, and crackers
11 Fatty foods like steak, bacon, hamburgers, cheeseburgers, pizza, and French fries
12 Sugary drinks like soda pop

When the following questions ask about "CERTAIN FOODS" please think of ANY food similar to those listed in the food group or ANY OTHER foods you have had a problem with in the past year

IN THE PAST 12 MONTHS:		Never	Once a month	2-4 times a month	2-3 times a week	4 or more times or daily
1.	I find that when I start eating certain foods, I end up eating much more than planned	0	1	2	3	4
2.	I find myself continuing to consume certain foods even though I am no longer hungry	0	1	2	3	4
3.	I eat to the point where I feel physically ill	0	1	2	3	4
4.	Not eating certain types of food or cutting down on certain types of food is something I worry about	0	1	2	3	4
5.	I spend a lot of time feeling sluggish or fatigued from overeating	0	1	2	3	4
6.	I find myself constantly eating certain foods throughout the day	0	1	2	3	4
7.	I find that when certain foods are not available, I will go out of my way to obtain them. For example, I will drive to the store to purchase certain foods even though I have other options available to me at home.	0	1	2	3	4
8.	There have been times when I consumed certain foods so often or in such large quantities that I started to eat food instead of working, spending time with my family or friends, or engaging in other important activities or recreational activities I enjoy.	0	1	2	3	4
9.	There have been times when I consumed certain foods so often or in such large quantities that I spent time dealing with negative feelings from overeating instead of working, spending time with my family or friends, or engaging in other important activities or recreational activities I enjoy.	0	1	2	3	4
10.	There have been times when I avoided professional or social situations where certain foods were available, because I was afraid I would overeat.	0	1	2	3	4
11.	There have been times when I avoided professional or social situations because I was not able to consume certain foods there.	0	1	2	3	4

12.	I have had withdrawal symptoms such as agitation, anxiety, or other physical symptoms when I cut down or stopped eating certain foods. (Please do NOT include withdrawal symptoms caused by cutting down on caffeinated beverages such as soda pop, coffee, tea, energy drinks, etc.)	0	1	2	3	4
13.	I have consumed certain foods to prevent feelings of anxiety, agitation, or other physical symptoms that were developing. (Please do NOT include consumption of caffeinated beverages such as soda pop, coffee, tea, energy drinks, etc.)	0	1	2	3	4
14.	I have found that I have elevated desire for or urges to consume certain foods when I cut down or stop eating them.	0	1	2	3	4
15.	My behavior with respect to food and eating causes significant distress.	0	1	2	3	4
16.	I experience significant problems in my ability to function effectively (daily routine, job/school, social activities, family activities, health difficulties) because of food and eating.	0	1	2	3	4

IN THE PAST 12 MONTHS:		NO	YES
17.	My food consumption has caused significant psychological problems such as depression, anxiety, self-loathing, or guilt.	0	1
18.	My food consumption has caused significant physical problems or made a physical problem worse.	0	1
19.	I kept consuming the same types of food or the same amount of food even though I was having emotional and/or physical problems.	0	1
20.	Over time, I have found that I need to eat more and more to get the feeling I want, such as reduced negative emotions or increased pleasure.	0	1
21.	I have found that eating the same amount of food does not reduce my negative emotions or increase pleasurable feelings the way it used to.	0	1
22.	I want to cut down or stop eating certain kinds of food.	0	1
23.	I have tried to cut down or stop eating certain kinds of food.	0	1
24.	I have been successful at cutting down or not eating these kinds of food	0	1

25. How many times in the past year did you try to cut down or stop eating certain foods altogether?	1 time	2 times	3 times	4 times	5 or more times

26. Please circle ALL of the following foods you have problems with:

Ice cream	Chocolate	Apples	Doughnuts	Broccoli	Cookies	Cake	Candy
White Bread	Rolls	Lettuce	Pasta	Strawberries	Rice	Crackers	Chips
Pretzels	French Fries	Carrots	Steak	Bananas	Bacon	Hamburgers	Cheese burgers
Pizza	Soda Pop	None of the above					

27. Please list any other foods that you have problems with that were not previously listed:

CET

Instructions

Listed below are a series of statements regarding exercise. Please read each statement carefully and circle the number that best indicates how true each statement is of you. Please answer all the questions as honestly as you can.

Never true	Rarely true	Sometimes true	Often true	Usually true	Always true
0	1	2	3	4	5

1)	I feel happier and/or more positive after I exercise.	0	1	2	3	4	5
2)	I exercise to improve my appearance.	0	1	2	3	4	5
3)	I like my days to be organised and structured of which exercise is just one part.	0	1	2	3	4	5
4)	I feel less anxious after I exercise.	0	1	2	3	4	5
5)	I find exercise a chore.	0	1	2	3	4	5
6)	If I feel I have eaten too much, I will do more exercise.	0	1	2	3	4	5
7)	My weekly pattern of exercise is repetitive.	0	1	2	3	4	5
8)	I do not exercise to be slim.	0	1	2	3	4	5
9)	If I cannot exercise I feel low or depressed.	0	1	2	3	4	5
10)	I feel extremely guilty if I miss an exercise session.	0	1	2	3	4	5
11)	I usually continue to exercise despite injury or illness, unless I am very ill or too injured.	0	1	2	3	4	5
12)	I enjoy exercising.	0	1	2	3	4	5
13)	I exercise to burn calories and lose weight.	0	1	2	3	4	5
14)	I feel less stressed and/or tense after I exercise.	0	1	2	3	4	5
15)	If I miss an exercise session, I will try and make up for it when I next exercise.	0	1	2	3	4	5
16)	If I cannot exercise I feel agitated and/or irritable.	0	1	2	3	4	5
17)	Exercise improves my mood.	0	1	2	3	4	5
18)	If I cannot exercise, I worry that I will gain weight.	0	1	2	3	4	5
19)	I follow a set routine for my exercise sessions e.g. walk or run the same route, particular exercises, same amount of time, and so on.	0	1	2	3	4	5
20)	If I cannot exercise I feel angry and/or frustrated.	0	1	2	3	4	5
21)	I do not enjoy exercising.	0	1	2	3	4	5
22)	I feel like I've let myself down if I miss an exercise session.	0	1	2	3	4	5
23)	If I cannot exercise I feel anxious.	0	1	2	3	4	5
24)	I feel less depressed or low after I exercise.	0	1	2	3	4	5

Barratt Impulsiveness Scale

DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly.

① Rarely/Never ② Occasionally ③ Often ④ Almost Always/Always

1	I plan tasks carefully.	①	②	③	④
2	I do things without thinking.	①	②	③	④
3	I make-up my mind quickly.	①	②	③	④
4	I am happy-go-lucky.	①	②	③	④
5	I don't "pay attention."	①	②	③	④
6	I have "racing" thoughts.	①	②	③	④
7	I plan trips well ahead of time.	①	②	③	④
8	I am self controlled.	①	②	③	④
9	I concentrate easily.	①	②	③	④
10	I save regularly.	①	②	③	④
11	I "squirm" at plays or lectures.	①	②	③	④
12	I am a careful thinker.	①	②	③	④
13	I plan for job security.	①	②	③	④
14	I say things without thinking.	①	②	③	④
15	I like to think about complex problems.	①	②	③	④
16	I change jobs.	①	②	③	④
17	I act "on impulse."	①	②	③	④
18	I get easily bored when solving thought problems.	①	②	③	④
19	I act on the spur of the moment.	①	②	③	④
20	I am a steady thinker.	①	②	③	④
21	I change residences.	①	②	③	④
22	I buy things on impulse.	①	②	③	④
23	I can only think about one thing at a time.	①	②	③	④
24	I change hobbies.	①	②	③	④
25	I spend or charge more than I earn.	①	②	③	④
26	I often have extraneous thoughts when thinking.	①	②	③	④
27	I am more interested in the present than the future.	①	②	③	④
28	I am restless at the theater or lectures.	①	②	③	④
29	I like puzzles.	①	②	③	④
30	I am future oriented.	①	②	③	④

Leeds Dependence Questionnaire - LDQ

Here are some questions about the importance of alcohol or other drugs in your life. Think about the main substance you have been using over the **last 4 weeks** and tick the closest answer to how you see yourself

	Never 0	Sometimes 1	Often 2	Nearly Always 3
Do you find yourself thinking about when you will next be able to have another drink or take more drugs?	☐	☐	☐	☐
Is drinking or taking drugs more important than anything else you might do during the day?	☐	☐	☐	☐
Do you feel that your need for drink or drugs is too strong to control?	☐	☐	☐	☐
Do you plan your days around getting and taking drink or drugs?	☐	☐	☐	☐
Do you drink or take drugs in a particular way in order to increase the effect it gives you?	☐	☐	☐	☐
Do you drink or take drugs morning, afternoon and evening?	☐	☐	☐	☐
Do you feel you have to carry on drinking or taking drugs once you have started?	☐	☐	☐	☐
Is getting an effect more important than the particular drink or drug you use?	☐	☐	☐	☐
Do you want to take more drink or drugs when the effects start to wear off?	☐	☐	☐	☐
Do you find it difficult to cope with life without drink or drugs?	☐	☐	☐	☐

NRES Committee South Central - Oxford A
Bristol Research Ethics Committee Centre
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BS1 2NT

Telephone: 0117 342 1331
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16 August 2013

Dr Rebecca Park
Clinical Senior Lecturer in Psychiatry
Department of Psychiatry,
University of Oxford.
Warneford Hospital
Oxford
OX3 7JX

Dear Dr Park

Study title: **Multimodal imaging in Anorexia Nervosa using fMRI and MEG: An investigation of Neural Networks, reward processing and habit formation during illness and after recovery.**
REC reference: **13/SC/0395**
IRAS project ID: **127207**

The Research Ethics Committee reviewed the above application at the meeting held on 02 August 2013. The committee would like to express its thanks to Ms Lauren Godier and Ms Jessica Scaife who attended to discuss the application.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Mr Thomas Fairman, nrescommittee.southcentral-oxforda@nhs.net.

Ethical Issues

Social and Scientific Value

- On the basis of the information provided the Committee was satisfied with this aspect of the proposed research.

Independent Review

2. On the basis of the information provided the Committee was satisfied with this

aspect of the proposed research.

Recruitment arrangements and access to health information

- The committee questioned what the researchers would do of a participant completed the online questionnaires but was then found to be unsuitable for participation, or decided not to consent to join the study.

The researchers confirmed that the data would be destroyed.

Favourable Risk Benefit Ratio

- On the basis of the information provided the Committee was satisfied with this aspect of the proposed research.

Care and protection of research participants

- The committee noted that the researchers planned to inform participants' GPs of their involvement in the study but had not submitted a GP letter for review. They requested that it be submitted.

The researchers confirmed that they will not be informing participants GP of their involvement in the study and will delete clause 5 from the consent form.

Informed Consent Process

- On the basis of the information provided the Committee was satisfied with this aspect of the proposed research.

Adequacy and completeness of participant information

- The committee noted that the PIS, in the 'MRI Scans' section of the PIS states that participants will be asked to sit down during the MRI scan and questioned the accuracy of this.

The researchers confirmed that participants would be asked to lie down during the MRI scanning procedure, and stated that they would correct this in the PIS.

Suitability of the Applicant and Supporting Staff

- On the basis of the information provided the Committee was satisfied with this aspect of the proposed research.

Other

- The committee questioned the relationship between this study and the Deep Brain Stimulation study submitted to the Oxford A committee for their meeting on the 7th June 2013. They questioned what the difference between the two studies was.

They noted that the deep brain stimulation study presupposes the existence of neural pathways while this study seeks to identify them and map them. The committee stated that, arguably, this study should be have been submitted first, to identify the pathways, and then the deep brain stimulation study submitted to manipulate them.

The researchers replied that, the deep brain stimulation study sought to manipulate the neural pathways while this study only sought to map them in greater detail.

- The committee advised that changes would be required to the consent form and that this would be detailed in the decision letter.

Decision – Favourable, with addition conditions

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

NHS Sites: The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

PIS

- In the 'MRI scans' section please correct the sentence 'you will be asked to sit quietly initially' to 'you will be asked to lie quietly initially'.

- In the 'What are the risks of taking part in the study' please delete the word 'also' from the sentence 'If you are pregnant you should also not take part'.

Consent

- Please delete clause 5.

- Please amend the formatting of the consent form so that the boxes line up with the relevant clauses so that participants are clear what they are consenting to.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering Letter		05 July 2013
Evidence of insurance or indemnity		01 August 2012
Interview Schedules/Topic Guides		05 July 2013
Letter from Sponsor		05 July 2013
Other: CV - Miss Lauren Godier		02 July 2013
Other: CV - Dr Rebecca Park		02 July 2013
Other: Review Process MRCCIC		21 March 2013
Other: Independent Peer Review MRCCIC		12 April 2013
Other: Letter from Funder - Award Letter imaging AN		11 March 2013
Other: Poster Advert	1	02 July 2013
Other: Email Advert	1	02 July 2013
Other: Daily Info Advert	1	02 July 2013
Other: LO Food Preference task: Cowdrey et al		30 January 2013
Other: DeWit: Habit learning tasks		29 August 2012
Other: Non NHS SSI Imaging An		05 July 2013
Participant Consent Form	1	02 July 2013
Participant Information Sheet	1	02 July 2013
Protocol	1	02 July 2013
Questionnaire: YBC-ED		
Questionnaire: AAQ-2		
Questionnaire: STA-Y		
Questionnaire: SHAPS		
Questionnaire: EDEQ6		

Questionnaire: BDI		
Questionnaire: CIA		
Questionnaire: RRS-ED		
Questionnaire: BIS		
Questionnaire: OCI-r		
Questionnaire: SPRSQ		
Questionnaire: CEQ		02 July 2013
Questionnaire: Starvation Dependence Q		02 July 2013
Questionnaire: OxBread Scale		02 July 2013
Questionnaire: Screening Questionnaire		02 July 2013
REC application	1	04 July 2013

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet. There were no declarations of interest.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments •
Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

13/SC/0395	Please quote this number on all correspondence

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

p.p. T. Fairman

Ms Alison Eden
Alternate Vice Chair

Email: nrescommittee.southcentral-oxforda@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*
"After ethical review – guidance for researchers"

Copy to: *Ms Heather House*

NRES Committee South Central - Oxford A

Attendance at Committee meeting on 02 August 2013

Committee Members:

Name	*Profession*	*Present*
Ms Raj Bains	Pharmacovigilance Business Consultant	No
Ms Jane Cheeseman	Research Nurse	Yes
Mr Stuart Cole	Online Retail Developer / Coordinator	Yes
Ms Alison Eden (Chaired the Meeting)	Publisher	Yes
Mrs Marion Fiddes	Consultant Project Manager	Yes
Dr Cynthia Graham	Senior Lecturer in Psychology	No
Mrs Lyndsay Hills	Retired Registered Nurse	Yes
Mrs Alison Kealy	Legal Assistant – Wills and Probate	Yes
Dr Karen Melham	Ethicist (Chair)	Yes
Dr Mohit Sharma	Speciality Registrar in Public Health	Yes
Mr Martin Usherwood	Retired Gynaecologist	Yes
Dr Sian Warriner	Consultant Midwife	Yes

Also in attendance:

Name	*Position (or reason for attending)*
Mr Thomas Fairman	Committee Coordinator

Written comments received from:

Name	*Position*
Mr Roy Sinclair	Retired Pharmacist

UNIVERSITY OF OXFORD
DEPARTMENT OF PSYCHIATRY

PARTICIPANT INFORMATION SHEET

Multimodal imaging of Neural Networks and Reward in Anorexia Nervosa

Principal Researcher*: Dr Rebecca Park, rebecca.park@psych.ox.ac.uk*
Co-investigator: *Professor Catherine Harmer: catherine.harmer@psych.ox.ac.uk*
DPhil student: Lauren Godier, lauren.godier@psych.ox.ac.uk

Part 1 tells you the purpose of this study and what will happen if you agree to take part.
Part 2 gives you more detailed information about the conduct of the study

Part 1:

You are being invited to take part in a research project. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read this information carefully and discuss it with friends, relatives and others if you wish. If there is anything you do not understand, or if you would like more information, please contact the researcher named above. Take time to decide whether you wish to take part.

What is the purpose of the study?

Anorexia Nervosa (AN) has the highest mortality of any psychiatric disorder and a lack of effective evidence based treatments. Better understanding of the processes underpinning AN is essential to help develop new treatments. This study aims to advance understanding of the neural processes involved in AN.

One particularly problem for people with AN is that extreme control of eating and weight becomes rewarding, but at the expense of normally rewards. These abnormal reward responses then seem to become habitual, compulsive and extremely hard to change, even when they cease to feel good. Our previous research in people with AN using behavioural tasks and functional magnetic resonance imaging (fMRI) suggests particular abnormalities in food reward processing and neural networks in the brain, which may underpin these problematic symptoms.

This study will further extend these findings using complimentary cutting edge neuroimaging strategies -Magnetoencephalography (MEG) and fMRI - together with tasks investigating reward and habit formation .

MEG and fMRI will be compared between individuals currently suffering from AN, individuals recovered from AN and healthy controls. Using MEG and fMRI as complimentary techniques will further understanding of neural processes underpinning AN, and inform the development of treatments targeting these processes. We include a food reward task to investigate food reward in AN under fMRI, and two behavioral tasks investigating aspects of habit formation. This will also allow us to examine associations between reward processing and habit formation and explore their neural basis.

We are therefore looking for **women currently suffering from AN**, **women recovered from AN** and **women who have never had an eating disorder** who are willing to attend three separate sessions at the Department of Psychiatry (Warneford Hospital), Oxford Centre for Human Brain Activity (OHBA, Warneford Hospital), and the Oxford Centre for Magnetic Resonance Imaging (OCMR, John Radcliffe Hospital).

Why have I been chosen?

You have received information about this study because either you have responded to an email or poster advertisement recruiting individuals for one of these groups: **women currently suffering from AN**, **women recovered from AN** and **women who have never had an eating disorder**

Do I have to take part?

No, **taking part is voluntary**. If you don't want to take part, you do not have to give a reason and no pressure will be out on you to try and change your mind. Not taking part in the study or withdrawing from the study will not affect any future health care you may seek. You will not be contacted again after the study unless you give consent for us to do so.

What will happen if I agree to take part?

If you agree to take part you will first be asked to complete a screening questionnaire and answer a few questions covering eligibility criteria to check if you are eligible to take part in the study . These will usually be done by email, but can be completed over the phone if you prefer

If you are eligible for the study you will be invited to complete an online questionnaire, consisting of a series of self-reports schedules which will take you around 30 minutes. The questions will cover psychological symptoms such as mood, anxiety, preoccupations and eating concerns. We ask you to do these online in order to reduce the time you need to spend in face to face sessions, but if your prefer this questionnaire can be done at the first session.

You will then be invited to attend three separate sessions at different sites : The first two sessions will be at the Warneford Hospital: the Department of Psychiatry and Oxford Centre for Human Brain Activity (OHBA) and the third session will be at the John Radcliffe Hospital -Oxford Centre for Magnetic Resonance Imaging (OCMR). These 3 sessions will last a total of 4 hours and will be arranged to occur over a 2 week period.

What will I have to do?

- Once we have confirmed you are eligible to take part in the study, we will send you an email link to an online questionnaire, consisting of a series of self-reports schedules which will take you around 30 minutes. The questions will cover psychological symptoms such as mood, anxiety, preoccupations and eating concerns. We ask you to do these online in order

to reduce the time you need to spend in face to face sessions, but if you prefer this on line questionnaire can be done at the first session.

- The first session will take place at the Department of Psychiatry, where we will arrange for you to be met by one of the researchers. During this visit you will have an interview covering current and past psychological symptoms. This interview will be digitally recorded in order to verify findings with the senior clinician in the research team, but once this is done it is then deleted. We will also ask you to fill out a few more questionnaires during the visit. This session will last 1.5- 2 hours.

- The second session will involve the MEG scan and afterwards completing two computer tasks. It will occur first thing in the morning after an overnight fast. We will arrange to meet you at the OHBA at where the scan will take place. You will be asked not to eat overnight prior to the MEG scan as we want everyone to be in a fasted condition. If you are on a meal plan, you should keep to this and we can arrange the timing of your scan so it does not interfere your eating. During the scan you will be asked to sit quietly in the scanner whilst MEG data is recorded in a no task resting state and then you will be asked to look at a series of pictures of food. This MEG scanning session will last a maximum of 30 minutes. You will then be asked to complete two computerised tasks and a pencil and paper task, in total taking 60 minutes. This second session will last around 1.5 hours**.**

  As you may want or need something to eat after the overnight fast we will offer you a snack breakfast before you leave, but this is totally optional and is not part of the study - or you are free to bring you own if you prefer.

- The third session will involve an MRI scan at the John Radcliffe Hospital. We will arrange to meet you at the OCMR where the scan will take place. You will be asked to refrain from food for 4 hours prior to the MRI scan. If you are on a meal plan we can arrange the scan so it does not interfere with this. During the scan you will initially be asked to sit quietly in the scanner whilst resting state brain activity, (with no task), is recorded. You will then be asked to complete a computerised task in the scanner, which will involve looking at pictures of food. Once out of the scanner you will be asked to complete a different computerised food pictures task. This session will last around 1 hour.

- An inconvenience allowance of £30 will be provided upon completion of the third session and reasonable travel expenses will be reimbursed after each session.

MEG Scans:
MEG scans are carried out at OHBA next to the Department of Psychiatry at the Warneford Hospital. Before the MEG scan, the researcher attaches sensors to the participant's wrists to measure their heartbeat and around their eyes to measure eye movements. The researcher also places small coils on the participant's forehead and above their ears to record their head position in the scanner. Participants can ask the researcher to stop at any time.

MEG scans measure direct electrical activity of the brain, and give a neural signature of the brains activity in real time. The MEG scanner is like a hat on your head, and you are seated during the scan. During the scan you will be asked to sit in the MEG chair whilst the receiver is placed over your head (this looks similar to a large old fashioned hairdryer at the

hairdressers). You will then be asked to sit quietly with your eyes closed whilst the MEG signal is recorded. You will be in contact with the researcher at all times during this session and will be able to stop it at any time for any reason.

MEG is a silent, non-invasive brain imaging technique that measures the magnetic fields produced by nerve cells. The MEG system contains very sensitive detectors arranged around a helmet shaped hollow. Brain activity is measured from a participant as they sit with their head inside this hollow. Because the magnetic signals produced by brain activity are tiny compared to those produced by the earth and electrical equipment, the scanner is in a specially built room that keeps out magnetic fields from the environment. MEG does not generate any magnetic fields and does not involve any ionising radiation. There are no known risks associated with MEG. MEG is a very sensitive technique and measurements can be affected by metal in the room. Participants will be asked to remove metallic objects that they are carrying or wearing, for example, jewellery, body piercings, removable dental braces and clothing with metal parts. Participants who wear glasses should inform the researcher in advance and they may be given special non-metallic glasses to wear.

Unexpected findings on your MEG scan
MEG research scans at OHBA are not appropriate for diagnostic purposes and researchers at OHBA are not trained to detect abnormal neural activity. In the unlikely event that abnormal neural activity is suspected with your MEG scan then the opinion of a clinically qualified specialist will be obtained. If the clinical specialist suspects abnormal neural activity, they will contact you to discuss the finding and request your permission to inform your GP. If any further investigations are necessary then these will occur within the NHS framework. MEG scans are not suitable for detecting structural abnormalities in your brain. No person associated with OHBA is responsible for the failure of an MEG research scan to detect an existing abnormality.

MRI scans:
For the MRI scans you will come to the OCMR at the John Radcliffe Hospital to have your brain scanned. When you arrive at the centre you would meet the researcher who will explain to you what would happen during the scan. The researcher would go through an MRI Safety Screening Form with you. This makes sure that you do not have any metal in your body and that it is safe for you to enter the scanner. Before the brain scan, you would be asked to remove any metal objects. This is because it is unsafe to take any metal objects into the scanner room where there is a strong magnetic field. The scanner is a large box with a tube running through the middle. You would lie on a bed, which moves into the centre of the tube, and a device shaped like a helmet would be put around your head. You would wear headphones to protect your hearing and so that you can listen to the researcher when spoken to. You will be able to see a screen at the end of the bed via a mirror on the helmet or via glasses. You would also be given a call button to hold throughout the scan. You can use this to get the attention of the researcher who will be on the other side of a window just outside the scanner room. You can speak to the researcher via a microphone from inside the scanner. It is very important that you keep still during the scans and try not to move your head at all. We would make sure that you were comfortable by providing cushions around your head and under your legs and a blanket if necessary. You will again be asked to sit quietly initially with your eyes closed whilst MRI is recorded. You will then be asked to complete a short task in the scanner.

Several types of imaging can be done during an MRI scan session, including structural MRI and functional MRI (fMRI). **Structural MRI** reveals the structure of the brain. **The Functional MRI** scan technique identifies changes in blood flow in different parts of the brain that are active when people perform simple cognitive or taste tasks designed to measure the way the brain deals with emotional/sensory information. fMRI uses the same methods that are used for Structural MRI brain scanning which provides detailed pictures of the brain.

Unexpected findings on your MRI scan
In the unlikely event of us seeing any structural abnormalities on your MRI scan, a designated clinical specialist will discuss the implications with you and arrange for further investigations as necessary. However, it is important to note that we do not carry out scans for diagnostic purposes, and therefore these scans are not a substitute for a clinical appointment. Rather, our scans are intended for research purposes only.

Exclusion Criteria:
You will not be eligible to take part if you have a history of head injury or neurological/serious medical illness. In addition, people who are left handed, under the age of 18 years or over the age of 60 years will not be able to take part, and those who are not sufficiently fluent in English. You will also be unable to take part if you are currently pregnant or likely to be pregnant.

MRI scanning should not be performed if you have a heart pacemaker, mechanical heart valve, mechanical implant such as an aneurysm clip, hip replacement, or if you carry pieces of metal that have accidentally entered your body. This is to ensure that we do not take the risk of metal being in your body when you go into the scanner. Also, it is not possible to wear normal glasses in the scanner. However, we can provide scanner-safe glasses for most prescriptions. Before going into each scanner the operator radiographer will go through the procedure with you and ensure that you are safe to go into the scanner (i.e. make sure you do not have a pacemaker etc).

In addition:
For the Control group: You will not eligible be if you have any current or past psychiatric illness. Your BMI must be within a normal range (18.5-25) and you must not have any first degree relatives with a current or past eating disorder diagnosis.

For the Recovered AN group: You will be eligible if you have not experienced significant eating disorder symptoms within the last year, and you must have a BMI within the normal range (18.5-25).

Current AN group: You will be unable to take part if you do not have a current diagnosis of AN.

What are the risks of taking part in the study?

- There are no known risks of MRI for most people. However, the use of magnets means that the scan procedure is not suitable for people with pacemakers, mechanical heart valves, hip replacements or with other metal implants in their body. Also, if you have ever sustained an eye injury involving metal or have any history of seizures you should not take part. If you

are pregnant you should also not take part. Women who are at risk of pregnancy may be asked to have a pregnancy test before taking part. If you suffer from claustrophobia or if you have suffered previously from anxiety in confined spaces, you may find sitting or lying still in the scanner unpleasant and it may be better not to take part.

- There are no known risks associated with MEG scanning. The procedure is silent and the sitting position is unlikely to cause any problems such as claustrophobia. In the unlikely event of us seeing any abnormalities on your MEG or MRI scan, a member of our research team will discuss the implications with you and, with your permission, your GP may be notified. However, it is important to note that we do not carry out our scans for diagnostic purposes, and therefore these scans are not a substitute for a clinical appointment. Rather, our scans are intended for research purposes only.

- Sometimes psychiatric screening reveals undiagnosed / unresolved eating or other psychiatric problems. If this is the case, you will be advised to contact your GP and will have the option of further advice from a senior clinical member of the research team. We are however unable to offer treatment as part of this research study.

- One of the computerised tasks will involve listening to loud noises, which you may find unpleasant. However, you will be in control of setting the volume of the noise prior to the task, and you will be able to terminate the task at any time you find the noise too unpleasant or loud.

Part 2 of the information sheet:

Will my taking part be confidential?

All the information you give us **will be confidential** and used for the purposes of this study only. The information collected during the study will be used in a way that will not allow you to be identified individually. The data will be collected and stored in accordance with the Data Protection Act 1998. Personal identifiers will be destroyed. Anonymised data will be stored on a password protected computer and any paper records will be stored in a locked filing cabinet.

Relevant sections of the records and data collected during the study may be looked at by responsible individuals from the University of Oxford and other regulatory bodies, where it is relevant to your taking part in this research.

What will happen to the study results?

The results will be analysed and submitted for publication in peer reviewed scientific journals. It should be emphasized that your name or any other information that would identify you will not be published. We will be happy to provide you with copies of the completed articles for you to keep and in addition, following completion of the study, a short summary of the study findings written in non-scientific language will be made available to participants on request.

Some of the results will also form part of one of the investigator's doctoral thesis. The University of Oxford is committed to the dissemination of its research for the benefit of society and the economy and, in support of this commitment, has established an online archive of research materials. This archive includes digital copies of student theses

successfully submitted as part of a University of Oxford postgraduate degree programme. Holding the archive online gives easy access for researchers to the full text of freely available theses, thereby increasing the likely impact and use of that research.

If you agree to participate in this project, part of the research will be written up as a thesis. On successful submission of the thesis, it will deposited both in print and online in the University archives, to facilitate its use in future research. The thesis will be published with embargoed access, meaning there will be a three year period in which public access is restricted. Once this period has lapsed, the thesis will be freely available for public access.

What will happen if I don't want to carry on with the study?
Participation is voluntary and you are free to withdraw at any time without giving any reason and without any medical care or legal rights being affected. However, data collected prior to withdrawal will be kept and may be included in the data analysis.

What if there is a problem?
If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact *Dr Rebecca Park: 01865226385, rebecca.park@psych.ox.ac.uk* or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224 or the head of CTRG, email ctrg@admin.ox.ac.uk .

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London, policy numbered :WD1200463)

Who has reviewed and approved this study?
All research in the NHS is looked at by an independent group of people called a Research Ethics Committee, to protect your interests. This study has been reviewed and approved by one of these Research Ethics Committees and by the University of Oxford Clinical Research Governence.

What about expenses and payment?
In recognition of your time and help you will receive an inconvenience allowance upon completion of session three of the study (£30). We will also cover any reasonable travel expenses, e.g. bus fares, parking costs.

Who is organising and funding the research?
This work is funded by the Medical Research Council and sponsored by the University of Oxford.

What do I do now?
Think about the information on this sheet, and contact the researcher if you are not sure about anything or would like more information. You will be asked to sign a consent form after you have had the opportunity to have any questions answered. The consent form will not be used to identify you. It will be filed separately from all other information.

For further information:
Dr Rebecca Park (Principal Researcher)
Department of Psychiatry

Warneford Hospital,
Oxford,
OX3 7DX
Rebecca.park@psych.ox.ac.uk / 01865 226385 (office hours only)

You can also seek independent general advice from the research information website 'Involve' – http://www.invo.org.uk/

THANK YOU FOR TAKING TIME TO READ THIS INFORMATION SHEET



University Of Oxford

Department of Psychiatry,
Warneford Hospital,
Oxford

Patient Consent Form REC No: 13/SC/0395

Version: 2 **Date: 10/9/2013**
Chief investigator: Dr Rebecca Park Patient Id No.:

Study title:

Please initial box

1. I confirm that I have read and understood the information sheet (Version 2 dated, 10/09/2013) for the above study and I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I confirm that I have had sufficient time to consider whether or not I want to be included in the study. ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
4. I understand that sections of any of my medical notes or trial data may be looked at by responsible individuals from the University of Oxford & Oxford University Hospitals NHS trust or Oxford health NHS trust where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
5. I agree to digital audio recording as part of my assessment. I understand that this will not be used for any other purpose other than diagnostic verification within the research team and will be deleted immediately afterwards. ☐
6. I agree that if abnormality is observed in my MEG or MRI data, this data and my identifying details may be viewed by clinical specialists and an MRI or MEG expert. I agree to a clinical neurologist contacting me to discuss medical concerns. ☐
7. I understand that my identifying details will be stored securely and that my permission will be sought before informing my GP of

University Of Oxford

Department of Psychiatry,
Warneford Hospital,
Oxford

any findings. I understand that this research is not suitable for diagnosing a medical condition and that I should consult my GP with my medical concerns. ☐

8. I agree to take part in the above study. ☐

_____	_____	_____
Name of patient	Date	Signature

_____	_____	_____
Name of Person taking consent	Date	Signature

Name of the researcher to be contacted if there are any problems:

Dr Rebecca Park : Department of Psychiatry 01865 223918 or 01865 226385

1 form for patient,
1 to be kept as part of the study documentation,
1 to be kept with Oxford Health NHS Foundation trust notes

NART (2nd edition)

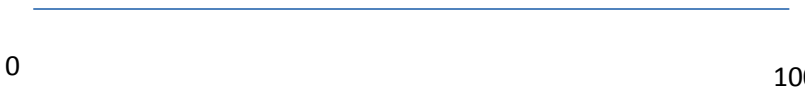
Verbal IQ = 129- (No. of Incorrect *0.919)

CHORD	SIMILIE
ACHE	BANAL
DEPOT	QUADRUPED
AISLE	CELLIST
BOUQUET	FAÇADE
PSALM	ZEALOT
CAPON	GAUCHE
DENY	TOPIARY
NAUSEA	LEVIATHAN
DEBT	BEATIFY
COURTEOUS	PRELATE
RAREFY	SIDEREAL
DRACHM	EQUIVOCAL
AEON	NAÏVE
PLACEBO	CATACOMB
ABSTEMIOUS	GOALED
DÉTENTE	THYME
IDYLL	HEIR
PUERPERAL	RADIX
AVER	ASSIGNATE
HIATUS	DEMESNE
PROCREATE	LABILE
GIST	CAMPANILE
SUPERFLUOUS	GOUGE

Visual Analogue Scales

Please place a mark on the line below to indicate how you feel at this moment in time.

I feel happy



I feel sad



I feel anxious



I am hungry



I am thirsty



I am full



I have the desire to eat



Visual Analogue Scales

Please place a mark on the line below to indicate how you feel at this moment in time.

Currently how do you see yourself in the mirror?

Very thin — Very fat

I am afraid of gaining weight

Not at all — Extremely

SPSRQ

1. Do you often refrain from doing something because you are afraid of it being illegal?	No	Yes
2. Does the good prospect of obtaining money motivate you strongly to do some things?	No	Yes
3. Do you prefer not to ask for something you are not sure you will obtain it?	No	Yes
4. Are you frequently encouraged to act by the possibility of being valued in your work, in your studies, with your friends or with your family?	No	Yes
5. Are you often afraid of new or unexpected situations?	No	Yes
6. Do you often meet people that you find physically attractive?	No	Yes
7. Is it difficult for you to telephone someone you do not know?	No	Yes
8. Do you like taking some drugs because of the pleasure you get from them?	No	Yes
9. Do you often renounce your rights when you know you can avoid a quarrel with a person or an organization?	No	Yes
10. Do you often do things to be praised?	No	Yes
11. As a child, were you troubled by punishments at home or in school?	No	Yes
12. Do you like being the center of attention at a party or a social meeting?	No	Yes
13. In tasks that you are not prepared for, do you attach great importance to the possibility of failure?	No	Yes
14. Do you spend a lot of your time on obtaining a good image?	No	Yes
15. Are you easily discouraged in difficult situations?	No	Yes
16. Do you need people to show their affection for you all the time?	No	Yes
17. Are you a shy person?	No	Yes

18. When you are with a group, do you try to make your opinions the most intelligent or the funniest?	No	Yes
19. Whenever possible, do you avoid demonstrating your skills for fear of being embarrassed?	No	Yes
20. Do you often take the opportunity to pick up people you find attractive?	No	Yes
21. When you are with a group, do you have difficulties selecting a good topic to talk about?	No	Yes
22. As a child, did you do a lot of things to get people's approval?	No	Yes
23. Is it often difficult for you to fall asleep when you think about things you have done or must do?	No	Yes
24. Does the possibility of social advancement, move you to action, even if this involves not playing fair?	No	Yes
25. Do you think a lot before complaining in a restaurant if your meal is not well prepared?	No	Yes
26. Do you generally give preference to those activities that imply an immediate gain?	No	Yes
27. Would you be bothered if you had to return to a store when you noticed you were given the wrong change?	No	Yes
28. Do you often have trouble resisting the temptation of doing forbidden things?	No	Yes
29. Whenever you can, do you avoid going to unknown places?	No	Yes
30. Do you like to compete and do everything you can do to win?	No	Yes
31. Are you often worried by things you said or did?	No	Yes
32. Is it easy for you to associate tastes and smells to very pleasant events?	No	Yes
33. Would it be difficult for you to ask your boss for a raise (salary increase)?	No	Yes
34. Are there a large number of objects or sensations that remind you of pleasant events?	No	Yes

35. Do you generally avoid speaking in public?	No	Yes
36. When you start to play with a slot machine, is it often difficult for you to stop?	No	Yes
37. Do you, on a regular basis, think that you could do more things if it was not for your insecurity or fear?	No	Yes
38. Do you sometimes do things for quick gains?	No	Yes
39. Comparing yourself to people you know, are you afraid of many things?	No	Yes
40. Does your attention easily stray from your work in the presence of an attractive stranger?	No	Yes
41. Do you often find yourself worrying about things to the extent that performance in intellectual abilities is impaired?	No	Yes
42. Are you interested in money to the point of being able to do risky jobs?	No	Yes
43. Do you often refrain from doing something you like in order not to be rejected or disapproved by others?	No	Yes
44. Do you like to put competitive ingredients in all of your activities?	No	Yes
45. Generally, do you pay more attention to threats than to pleasant events?	No	Yes
46. Would you like to be a socially powerful person?	No	Yes
47. Do you often refrain from doing something because of your fear of being embarrassed?	No	Yes
48. Do you like displaying your physical abilities even though this may involve danger?	No	Yes

Beck's Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

1.
   0 I do not feel sad.
   1 I feel sad
   2 I am sad all the time and I can't snap out of it.
   3 I am so sad and unhappy that I can't stand it.
2.
   0 I am not particularly discouraged about the future.
   1 I feel discouraged about the future.
   2 I feel I have nothing to look forward to.
   3 I feel the future is hopeless and that things cannot improve.
3.
   0 I do not feel like a failure.
   1 I feel I have failed more than the average person.
   2 As I look back on my life, all I can see is a lot of failures.
   3 I feel I am a complete failure as a person.
4.
   0 I get as much satisfaction out of things as I used to.
   1 I don't enjoy things the way I used to.
   2 I don't get real satisfaction out of anything anymore.
   3 I am dissatisfied or bored with everything.
5.
   0 I don't feel particularly guilty
   1 I feel guilty a good part of the time.
   2 I feel quite guilty most of the time.
   3 I feel guilty all of the time.
6.
   0 I don't feel I am being punished.
   1 I feel I may be punished.
   2 I expect to be punished.
   3 I feel I am being punished.
7.
   0 I don't feel disappointed in myself.
   1 I am disappointed in myself.
   2 I am disgusted with myself.
   3 I hate myself.
8.
   0 I don't feel I am any worse than anybody else.
   1 I am critical of myself for my weaknesses or mistakes.
   2 I blame myself all the time for my faults.
   3 I blame myself for everything bad that happens.

9.

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10.

0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11.

0 I am no more irritated by things than I ever was.
1 I am slightly more irritated now than usual.
2 I am quite annoyed or irritated a good deal of the time.
3 I feel irritated all the time.

12.

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

13.

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions more than I used to.
3 I can't make decisions at all anymore.

14.

0 I don't feel that I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel there are permanent changes in my appearance that make me look unattractive
3 I believe that I look ugly.

15.

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16.

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18.

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19.

0 I haven't lost much weight, if any, lately.
1 I have lost more than five pounds.
2 I have lost more than ten pounds.
3 I have lost more than fifteen pounds.

20.

0 I am no more worried about my health than usual.
1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think of anything else.

21.

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I have almost no interest in sex.
3 I have lost interest in sex completely.

STA-Y

INSTRUCTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and circle an answer to indicate how you feel *right now*, that is, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement, but give the answer which seems to describe your present feelings best.

		Not at all	Somewhat	Moderately so	Very Much so
1.	I feel calm	0	1	2	3
2.	I feel secure	0	1	2	3
3.	I am tense	0	1	2	3
4.	I feel strained	0	1	2	3
5.	I feel at ease	0	1	2	3
6.	I feel upset	0	1	2	3
7.	I am presently worrying over possible misfortunes	0	1	2	3
8.	I feel satisfied	0	1	2	3
9.	I feel frightened	0	1	2	3
10.	I feel comfortable	0	1	2	3
11.	I feel self-confident	0	1	2	3
12.	I feel nervous	0	1	2	3
13.	I am jittery	0	1	2	3
14.	I feel indecisive	0	1	2	3
15.	I am relaxed	0	1	2	3
16.	I feel content	0	1	2	3
17.	I am worried	0	1	2	3
18.	I feel confused	0	1	2	3
19.	I feel steady	0	1	2	3
20.	I feel pleasant	0	1	2	3

TAI-Y

INSTRUCTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then circle an answer sheet to indicate how you generally feel. There are no right or wrong answers. Do not spend too much time on any one statement, but give the answer which seems to describe how you generally feel.

		Almost Never	Sometimes	Often	Almost Always
1.	I feel pleasant	0	1	2	3
2.	I feel nervous and restless	0	1	2	3
3.	I feel satisfied with myself	0	1	2	3
4.	I wish I could be as happy as others seem to be	0	1	2	3
5.	I feel like a failure	0	1	2	3
6.	I feel rested	0	1	2	3
7.	I am "calm, cool, and collected"	0	1	2	3
8.	I feel that difficulties are piling up so that I cannot overcome them	0	1	2	3
9.	I worry too much over something that really doesn't matter	0	1	2	3
10.	I am happy	0	1	2	3
11.	I have disturbing thoughts	0	1	2	3
12.	I lack self-confidence	0	1	2	3
13.	I feel secure	0	1	2	3
14.	I make decisions easily	0	1	2	3
15.	I feel inadequate	0	1	2	3
16.	I am content	0	1	2	3
17.	Some unimportant thought runs through my mind and bothers me	0	1	2	3
18.	I take disappointments so keenly that I can't put them out of my mind	0	1	2	3
19.	I am a steady person	0	1	2	3
20.	I get in a state of tension or turmoil as I think about my recent concerns and interests	0	1	2	3

OCI-R

The following statements refer to experiences that many people have in their everyday lives. Circle the number that best describes **HOW MUCH** that experience has **DISTRESSED or BOTHERED you during the PAST MONTH.** The numbers refer to the following verbal labels:

0 Not at all	1 A little	2 Moderately	3 A lot	4 Extremely

1.	I have saved up so many things that they get in the way.	0 1 2 3 4
2.	I check things more often than necessary.	0 1 2 3 4
3.	I get upset if objects are not arranged properly.	0 1 2 3 4
4.	I feel compelled to count while I am doing things.	0 1 2 3 4
5.	I find it difficult to touch an object when I know it has been touched by strangers or certain people.	0 1 2 3 4
6.	I find it difficult to control my own thoughts.	0 1 2 3 4
7.	I collect things I don't need.	0 1 2 3 4
8.	I repeatedly check doors, windows, drawers, etc.	0 1 2 3 4
9.	I get upset if others change the way I have arranged things.	0 1 2 3 4
10.	I feel I have to repeat certain numbers.	0 1 2 3 4
11.	I sometimes have to wash or clean myself simply because I feel contaminated.	0 1 2 3 4
12.	I am upset by unpleasant thoughts that come into my mind against my will.	0 1 2 3 4
13.	I avoid throwing things away because I am afraid I might need them later.	0 1 2 3 4
14.	I repeatedly check gas and water taps and light switches after turning them off.	0 1 2 3 4
15.	I need things to be arranged in a particular way.	0 1 2 3 4
16.	I feel that there are good and bad numbers.	0 1 2 3 4
17.	I wash my hands more often and longer than necessary.	0 1 2 3 4
18.	I frequently get nasty thoughts and have difficulty in getting rid of them.	0 1 2 3 4

YBC-EDS

Recent research has shown that preoccupations and rituals commonly occur among people with eating disorders. While completing the checklist below, please keep in mind our definitions of preoccupations and rituals.

Preoccupations are *ideas, thoughts, images or impulses that repeatedly enter your mind. They may seem to occur against your will.*

Examples of preoccupations might include excessive concern with your body shape, and/or excessive concern about the caloric content of food.

Preoccupations differ from worries or concerns. Worries or concerns tend to just occur from time to time and usually do not affect your life very much, whereas preoccupations may enter your mind so frequently that they interfere with one or more areas of your life.

Rituals on the other hand, are *behaviors or acts that you feel driven to perform.* At times, you may try to resist doing them but this may prove difficult. You may experience anxiety that does not diminish until the behavior is completed.

An example of a ritual is the need to compute the exact caloric content of all of the foods you consume. While most rituals are observable behaviors, some are unobservable mental acts, such as silently computing the caloric content of foods, or having to recite nonsense phrases to yourself each time you think of food.

Rituals, as we define them here, should not be confused with habits, which most people have. Habits (e.g., brushing your teeth before washing your face) are routines performed in a similar way. However, rituals are accompanied with a sense that the activity *must* be performed in a precise manner. Altering or being unable to perform a ritual often leads to very unpleasant or anxious feelings.

Please keep the above definitions in mind as you complete the checklist below. Please read each item on the checklist carefully and place a checkmark beside each preoccupation and ritual that applies to you in BOTH of the categories that are described below (i.e., Current and Worst):

1) Current: Place a checkmark in this column for any preoccupations and/or rituals that you currently experience (i.e., over the past month, including today).
    a. For inpatients, your "Current Period" is the one month period prior to your hospitalization.
2) Worst: Place a checkmark in this column for any preoccupations and/or rituals that you have experienced during your worst period. Your "Worst Period" is defined as the one-month period of time during which your eating disorder symptoms were at their worst.
    a. For inpatients, do NOT consider the time when you were in the hospital as your worst period. Instead, consider your "Worst Period" to be any one-month time period of time outside of the hospital during which your eating disorder symptoms were at their worst.

Please note that for some individuals, the "Current Period" may be the same time period as the "Worst Period." For others, the "Current" and "Worst" periods may be different periods of time. *If your "Current Period" and "Worst Period" are the same period of time, please place a checkmark in both columns (i.e., Current and Worst) for those preoccupations and rituals that are relevant for you.*

Please identify your Current and Worst periods below:

"Current Period": Date range that defines the past month
"Worst Period": Date range that defines your worst one-month period of symptoms (e.g., month of September during 9th grade at age 14)

Current Period (date range):

Worst Period (date range):

Is your Current Period the same as your Worst Period? Yes No

Preoccupations

Current	Worst	
		Food Preoccupations
1)_____	_____	Categorize all foods as "good" or "bad"
2)_____	_____	Think excessively about the fat content of food
3)_____	_____	Think excessively about the caloric content of food
4)_____	_____	Think excessively about the carbohydrate/sugar content of food
5)_____	_____	Fear that eating certain types of food will lead to immediate body changes (e.g., eating fat will deposit fat onto your hips)
		Eating Preoccupations
1)_____	_____	Fear of eating from a full plate of food
2)_____	_____	Fear of eating all of the food that is on a plate of food
3)_____	_____	Fear of consuming fluids
4)_____	_____	Fear of not being able to consume fluids
5)_____	_____	Fear of being unable to eat
6)_____	_____	Fear of being unable to stop or control the amount you are eating
7)_____	_____	Fear of eating in front of other people
		Weight and Shape Preoccupations
1)_____	_____	Fear of being fat or overweight
2)_____	_____	Fear of weighing outside of a narrow range of weights, or preoccupation with a specific weight
3)_____	_____	Excessive concern with a specific body part or aspect

of your appearance

4)_____ _____ Fear of others thinking you are fat

Clothing Preoccupations

1)_____ _____ Excessive concern with a particular size of clothing (e.g. will not buy clothing that is not a specific size even if it fits)

2)_____ _____ Fear of wearing certain types of clothing (e.g. fear of wearing underwear or bathing suit).

3)_____ _____ Fear or wearing tight or loose fitting clothes.

Miscellaneous Preoccupations

1)_____ _____ Preoccupations about hoarding food (e.g. collecting, hiding, or stashing food).

2)_____ _____ Preoccupations about exercising.

Rituals

Current **Worst**

Eating Rituals

1)_____ _____ Need to consume food at a specific rate (e.g. can only take a bite every 2 minutes).

2)_____ _____ Need to chew each mouthful of food a specific number of times.

3)_____ _____ Need to cut each piece of food into a specific size.

4)_____ _____ Need to consume only certain colors or types of food.

5)_____ _____ Need to avoid certain types of food (e.g. fats or meats).

6)_____ _____ Need to consume each type of food on your plate

completely and in a specific order (e.g. must eat all of your vegetables before you eat your potatoes).

7)_____ _____ Need to consume fluids in a certain way or amount (e.g. need to drink 2 glasses or water before each meal).

8)_____ _____ Need to eat meals by yourself.

9)_____ _____ Needs to leave food on the plate when done eating: cannot consume all the food on your plate.

10)____ _____ Need to manipulate or stir your food (e.g. play with your food whilst eating).

11)____ _____ Need to fill your glass or plate only partially.

12)____ _____ Needs to have the table set in a specific way before you can eat.

13)____ _____ Need to wipe mouth with a napkin a fixed number of times after each bite of food.

14)____ _____ Need for food not to touch your lips while eating.

15)____ _____ Need for no part of your body to touch the table or plate whilst eating.

16)____ _____ Need for absolute constancy of food expected (e.g. an orange would not do if you were expecting an apple).

Food Rituals

1)_____ _____ Need to compute the caloric content of all foods eaten.

2)_____ _____ Need to compute the fat content of all food eaten.

3)_____ _____ Need to cook for others in a ritualized way.

Bingeing Rituals*

*Note: "Binges" are episodes of eating that some people experience. They are defined by eating what most would consider to be a large amount of food in 2 hours or less, while experiencing a loss of control (i.e., feeling that you cannot stop eating, or control what or how much you are eating)...

1)_____	_____	Need to begin each binge with a certain type of food or with a food of a certain color.
2)_____	_____	Need to eat only certain types of food during a binge.
3)_____	_____	Need to eat all food that is present (i.e. can leave no food uneaten during a binge).

Purging Rituals*

*Note: "Purging" refers to behaviours that some people engage in in an attempt to influence weight or shape and/or to counteract the effects of overeating. Purging behaviours include self-induced vomiting and/or laxative, diuretic or enema misuse.

1)_____	_____	Need to purge in a specific way or position (e.g. must use 2 fingers while inducing vomiting).
2)_____	_____	Need to purge a specific minimum amount.
3)_____	_____	Need to purge within a specific amount of time after eating.
4)_____	_____	Need to purge in a specific place.

Body Rituals

1)_____	_____	Need to have thighs NOT touch while sitting or standing.
2)_____	_____	Need to continually check that wrist can be spanned with your fingers.

3)_____ _____ Need to feel hip bones repeatedly.

4)_____ _____ Need to feel specific bone (e.g. collar bone or ribs).

5)_____ _____ Ritualised bathroom habits (e.g. pushing on your lower stomach while urinating or defecating).

6)_____ _____ Need to overdress in order to force yourself to sweat.

Weight Rituals

1)_____ _____ Need to repeatedly weigh yourself.

2)_____ _____ Need to weigh yourself in a ritualized way (e.g. at a specific time of day, or just after eating).

Exercise Rituals

1)_____ _____ Need to exercise after meals.

2)_____ _____ Need to exercise in a specific way or at a specific time.

3)_____ _____ Ritualized exercise pattern (e.g. must do 50 sit-ups if interrupted at 49, must begin all over again).

4)_____ _____ Need to be moving at all times (e.g. pacing, fidgeting).

5)_____ _____ Need to shiver to expend calories, instead of putting on additional clothing when cold.

Hoarding/Saving Rituals

1)_____ _____ Hoarding food in a ritualized way (e.g. hiding food in your bedroom).

2)_____ _____ Collecting and saving pictures of food, articles on food or recipes.

Listmaking Rituals

1)_____ _____ Making lists of body weight.

2)_____ _____ Making lists of foods eaten and/or calories consumed.

Thank you for taking the time to complete the YBC-EDS checklist. Now please proceed to the next section, below, in order to answer the questions about your preoccupations and rituals.

If you have not checked off any preoccupations or rituals, you are now finished with the scale. Thank You!

YBC-EDS

Preoccupations

Now that you have identified your preoccupations during your Current and Worst periods, please keep those items in mind as you answer the next 9 questions (i.e., questions 1-9).

As a reminder, your "Current Period" is defined as the past month, including today. (For inpatients, think about the one-month period prior to your hospitalization.) Your "Worst Period" is defined as the one-month period of time during which your eating disorder symptoms were at their worst. (For inpatients, do NOT consider the time when you were in the hospital as your Worst Period. Instead, consider your "Worst Period" to be any one-month period of time outside of the hospital during which your eating disorder symptoms were at their worst.)

Please rate each of the following 9 items for BOTH your Current Period and your Worst Period. Using the Oto 4 rating scales under each question, please fill in only ONE numerical rating for "Current" and ONE numerical rating for "Worst."

Please define your Current and Worst Periods below. *(Note: These should be the same as the time periods you defined previously.):*

Current Period (date range): _

Worst Period (date range):

If your "Current Period" and "Worst Period" are the same period of time, please place a numerical rating in both the "Current" and "Worst" columns.

1. _____ _____

Current Worst

How much of your time, including meal times, was occupied by preoccupations?

0 =None

1 = Less than 1 hour a day (occur no more than 8 times a day)

2= between 1 and 3 hours a day (occur more than 8 times a day)

3= More than 3 and up to 8 hours a day (occur more than 8 times a day)

4= Greater than 8 hours a day (too numerous to count)

2. _____ _____

Current Worst

On average, what is the longest block of time in which preoccupations are absent?

0 =No preoccupations

1 = More than 8 consecutive waking hours a day

2= More than 3 and up to 8 consecutive hours a day

3= More than 1 and less than 3 consecutive hours a day

4= Less than 1 consecutive hour a day

3. _____ _____

Current Worst

How much of your preoccupations interfere with your social or work/school functioning?

0 =No interference

1 = Mild interference with activities (e.g. social, school or work) but overall performance not impaired.

2= Moderate impairment with activities (e.g. social, school or work) but still manageable.

3= Severe interference, causes substantial impairment.

4= Extreme interference, incapacitating.

4. _____ _____

Current Worst

How much distress do your preoccupations cause you?

0 =None

1= Mild, not very disturbing.

2= Moderate, disturbing, but still manageable.

3= Severe, very disturbing.

4= Extreme, near constant and disabling distress.

5. _____ _____

Current Worst

Are these preoccupations consistent with the way you see yourself?

0 =No, they are not at all a part of who I am

1= Mostly not a part of who I am

2= They are somewhat a part and somewhat not a part of who I am

3= They are a part of me, but not completely

4= Yes, they are completely a part of who I am.

6. _____ _____

Current Worst

How often do you try to resist these preoccupations as they enter your mind?

0 = Always try to resist, or symptoms are so minimal you do not feel the need to try and resist them.

1= Try to resist most of the time (i.e. more than half of the time).

2= Try to resist some of the time

3= Never try to resist, but do give in reluctantly

4= Never try to resist, willingly yield to all preoccupations

7. _____ _____

Current Worst

How much control do you have over your preoccupations?

0 = Complete control

1 = Much control, usually able to stop or divert preoccupations with some effort and concentration.

2= Moderate control, sometimes able to stop or divert preoccupations.

3= Little control, rarely successful in stopping or diverting preoccupations.

4= No control, rarely able to even momentarily alter thinking.

8. _____ _____

Current Worst

Are your preoccupations reasonable or make sense to you?

0 = Not at all, the preoccupations are senseless and excessive, or the preoccupations are minimal.

1 = Not much sense, I see the absurdity or excessiveness of the preoccupations.

2= Somewhat yes and somewhat no.

3= Yes, the preoccupations mostly make sense.

4= Yes, the preoccupations make complete sense.

9. _____ _____

Current Worst

How much effort would you be willing to expend to stop these preoccupations?

0 = I would do just about anything to stop them, or the preoccupations are so minimal that you do not feel the need to stop them.

1 = I would be willing to do some work to stop the preoccupations.

2= Somewhat. I would like to be bothered less by the preoccupations but would not be willing to put much effort toward that goal.

3= I would make almost no effort to stop the preoccupations.

4= I would not do anything to stop the preoccupations, at times they are comforting and reassuring to me.

Rituals

Now that you have identified your rituals during your Current and Worst periods, please keep those items in mind as you answer the next 9 questions (i.e., questions 10-18).

As a reminder, your "Current Period" is defined as the past month, including today. (For inpatients, think about the one-month period prior to your hospitalization). Your "Worst Period" is defined as the one-month period of time during which your eating disorder symptoms were at their worst. (For inpatients, do NOT consider the time when you were in the hospital as your Worst Period. Instead, consider your "Worst Period" to be any one-month time period of time outside of the hospital during which your eating disorder symptoms were at their worst.)

Please rate each of the following 9 items for BOTH your Current Period and your Worst Period. Using the Oto 4 rating scales under each question, please fill in only ONE numerical rating for "Current" and ONE numerical rating for "Worst."

Please define your Current and Worst Periods below. *(Note: These should be the same as the time periods you defined previously.):*

Current Period (date range):

Worst Period (date range):

If your "Current Period" and "Worst Period" are the same period of time, please place a numerical rating in both the "Current" and "Worst" columns.

10. _____ _____

Current Worst

How much of your time was spent performing rituals?

0 =None

1 = Less than 1 hour a day (occur no more than 8 times a day)

2= between 1 and 3 hours a day (occur more than 8 times a day)

3= More than 3 and up to 8 hours a day (occur more than 8 times a day)

4= Greater than 8 hours a day (too numerous to count)

11. _____ _____

Current Worst

On average, what is the longest block of time in which riatuls are absent?

0 =No rituals

1 = More than 8 consecutive waking hours a day

2= More than 3 and up to 8 consecutive hours a day

3= More than 1 and less than 3 consecutive hours a day

4= Less than 1 consecutive hour a day

12. _____ _____

Current Worst

How much of your rituals interfere with your social or work/school functioning?

0 =No interference

1 = Mild interference with activities (e.g. social, school or work) but overall performance not impaired.

2= Moderate impairment with activities (e.g. social, school or work) but still manageable.

3= Severe interference, causes substantial impairment.

4= Extreme interference, incapacitating.

13. _____ _____

Current Worst

How anxious would you feel if prevented from performing your rituals?

0 =None

1= Mild, slight anxiety if prevented.

2= Moderate, anxiety would mount but remain manageable until rituals could be performed.

3= Severe, very disturbing increase in anxiety.

4= Extreme, incapacitating anxiety.

14. _____ _____

Current Worst

Are these rituals consistent with the way you see yourself?

0 = No, they are not at all a part of who I am

1= Mostly not a part of who I am

2= They are somewhat a part and somewhat not a part of who I am

3= They are a part of me, but not completely

4= Yes, they are completely a part of who I am.

15. _____ _____

Current Worst

How often do you try to resist these rituals?

0 = Always try to resist, or symptoms are so minimal you do not feel the need to try and resist them.

1= Try to resist most of the time (i.e. more than half of the time).

2= Try to resist some of the time

3= Never try to resist, but do give in reluctantly

4= Never try to resist, willingly yield to all rituals

16. _____ _____

Current Worst

How much control do you have over your preoccupations?

0 = Complete control

1 = Much control, usually able to exercise control over rituals with some effort and concentration.

2= Moderate control, can control them with difficulty.

3= Little control, can delay only with difficulty.

4= No control, rarely able to even momentarily delay activity.

17. _____ _____

Current Worst

Are your rituals reasonable or make sense to you?

0 = Not at all, the rituals are senseless and excessive, or the rituals are minimal.

1 = Not much sense, I see the absurdity or excessiveness of the rituals.

2= Somewhat yes and somewhat no.

3= Yes, the rituals mostly make sense.

4= Yes, the rituals make complete sense.

18. _____ _____

Current Worst

How much effort would you be willing to expend to stop these rituals?

0 = I would do just about anything to stop them, or the rituals are so minimal that you do not feel the need to stop them.

1 = I would be willing to do some work to stop the rituals.

2= I would not be willing to put much effort towards stopping the rituals.

3= I would make almost no effort to stop the rituals.

4= I would not do anything to stop the rituals, at times they are comforting and reassuring to me.

*Please note: This is the last question on the scale. When answering this last question (i.e., question 19), please consider both the preoccupations and rituals that you checked off on your checklists (pages 2-7), during the time periods you defined as your "Current" and "Worst" periods.

If your "Current Period" and "Worst Period" are the same period of time, please place a numerical rating in both the "Current" and "Worst" columns.

19. _____ _____

Current Worst

How much have you avoided doing anything, going any place, or being with anyone because of your preoccupations or out of concern you will perform your rituals?

0 = No deliberate avoidance

1 = Mild, minimal avoidance

2= Moderate, some avoidance clearly present.

3= Severe, much avoidance.

4= Extreme, very extensive avoidance.

You are now finished with the questionnaire. Thank You!

VAS scale ratings across groups and task

	Noise Avoidance Task						Slips-Of-Action Task					
VAS	**AN-C (n=13)**		**AN-R (n=14)**		**HC (n=17)**		**AN-C (n=13)**		**AN-R (n=14)**		**HC (n=17)**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Happiness	51.0	27.1	57.2	26.2	73.9	17.2	51.5	27.1	61.1	20.6	72.8	15.1
Despondence	31.0	28.4	27.4	22.2	19.0	10.1	32.4	28.9	23.2	21.1	19.1	18.3
Anxiety	31.6	21.4	22.9	20.1	20.9	23.3	48.7	21.0	21.4	16.2	17.2	18.0
Hunger	49.6	26.3	61.1	26.3	77.0	16.3	46.2	24.8	53.6	27.6	76.5	15.2
Thirst	51.0	30.6	53.7	25.1	64.2	22.5	51.9	23.5	52.7	30.1	61.2	24.6
Fullness	34.4	31.7	22.1	29.0	16.2	13.5	33.3	32.3	20.6	24.0	9.1	10.4
Desire to eat	42.8	29.2	65.6	26.5	77.5	15.3	43.9	28.4	60.4	29.1	81.1	12.8
Feelings of fatness	57.3	27.2	56.4	13.6	46.0	14.6	57.2	27.2	53.1	9.2	45.9	13.9
fear of fatness	76.8	18.9	55.9	25.3	31.9	19.4	76.3	18.9	54.9	22.8	32.6	21.8

Overview of MEG

MEG is the non-invasive measurement of the magnetic fields generated in the brain in real time. MEG, and similarly EEG, has unrivalled temporal resolution, although both suffer limitations in spatial resolution as signals are recorded from the scalp. This section will give a brief overview of the electrophysiological basis of MEG signals, measurement of MEG signals, strength and limitations of MEG relative to other neuroimaging techniques, and analysis approaches, with particular focus on the beamforming techniques used in Chapter 5 of this thesis.

The electrophysiological basis of MEG

MEG signals are generally accepted to be generated by the synchronous neuronal activity of thousands of neurons. These neurons generate time-varying electrical currents when activated, and these currents can be distinguished into two types: action potentials, and postsynaptic potentials. Action potentials are thought to make a minimal contribution to the magnetic fields measured by MEG. This is because the probability of synchronous action potentials at a measurable level is low, since they are extremely brief and their influence on recordings attenuates at a distance. It is generally accepted that slower postsynaptic potentials are the main contributor to MEG signals. These can be further split into excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs). EPSPs are generated by the flow of positive ions into the cell membrane, resulting in a positive electrical current being directed into the extracellular medium. In contrast, IPSPs can result from negative ions flowing inwards, or positive ions flowing outwards, resulting in the positive electrical current flowing out of the neuron. Both EPSPs and IPSPs result in a compensatory extracellular current flowing in the opposite direction. The synchronous flow of these intracellular currents gives rise to magnetic fields measured outside the scalp in MEG.

The main neuronal population that gives rise to the measured magnetic fields are the pyramidal neurons of the cortex, which are situated perpendicular to the cortical surface. Bundles of these neurons in the sulci of the folded cortex are oriented tangentially to the scalp. The activity of these creates magnetic fields outside the head, following the 'right hand rule' of electromagnetism. This rule posits that magnetic field lines around a long wire carrying an electric current will form concentric circles around that wire, and the direction of the field will be perpendicular to the wire. This is analogous to the direction of the fingers on your right hand, if you wrapped your hand around the wire. It has been calculated that about 50,000 of these pyramidal cells would need to be active synchronously to produce a measurable magnetic field. These synchronous neurons act as a 'current dipoles', which can be measured by MEG sensors near the scalp. However, these synchronised neuronal current induce only very weak magnetic fields, about 10 femtotesla, which is considerably smaller than environmental noise (about 10^8 femtotesla). This makes detection of this weak magnetic field challenging in the presence of competing environmental noise.

Measurement of MEG signals

The measurement of MEG signals takes advantage of the superconducting properties of some materials, which at very low temperatures lose all electrical resistance. This allows an electrical current to flow infinitely when these materials are arranged in a loop. MEG systems use sensitive Superconducting Quantum Interference Devices (SQUIDs), made of these superconducting materials immersed in liquid helium, to measure the weak magnetic fields emitted by the brain. Small breaks in the loops that make up the SQUIDS, or 'Josephson Junctions', create a measurable dynamic resistance across the SQUID when a constant current is fed through. This allows the measurement of alterations in average voltage across the SQUID, which are caused by changes in the magnetic flux (net magnetic field

across the SQUID). However, we are unable to use the output of the SQUID directly, as this only emits a periodic response. Instead, variation in the output of the SQUID, caused by changes in magnetic flux, is compensated for with an artificially generated negative feedback signal, and as such is held constant. It is this negative feedback signal, which linearly tracks the true signal, which is recorded by the MEG system.

SQUIDs are coupled with flux transformers, which allow more magnetic flux to be measured by the small SQUIDs (which are often only 1mm in diameter), to form the sensor coils used in MEG sensor arrays. Magnetometers are the simplest configuration, with a single pick up coil, which measures the magnetic component perpendicular to the coil surface. However these are sensitive to both near and distant signal sources. Gradiometers make use of an additional distant compensation coil, decreasing interference from far away sources, which should be homogenous across the pick-up and compensation coil. A typical MEG system has several hundred sensors surrounding the head shaped recess, and is housed in a magnetically shielded room in order to reduce interference from ambient magnetic noise.

Pre-processing of MEG data

The purpose of data pre-processing in MEG is to enhance the signals of interest, whilst attenuating noise or rejecting episodes in the recordings with high levels of artifact. Digital band pass filtering is often applied first to extract signals within a certain frequency range of interest. However, within this extracted frequency range there is still likely to be a wide variety of artefacts. These include signals from other sources in the brain, as well as signals created by movement of the eyes, heart and other muscles. There may also be external electromagnetic noise created by other devices used in the experiment or within the surrounding environment. Electrophysiological monitoring and the use of additional sensors away from head to capture environmental magnetic fields allows for artifact templates to be

created. These artefacts, which are considered to be independent of the brain processes being investigated, can be reduced with statistics that use representative events, such as eye-blinks and heartbeats, to identify perturbations caused by these events in the data. Other approaches such as principal components analysis and independent components analysis can also be used to identify components in the data not thought to be generated by the brain processes of interest.

Approaches to source analysis in MEG

The aim of source analysis in MEG is to determine the location of activity within the brain, from the induced magnetic fields that are measured outside the scalp. In this way, source analysis in MEG suffers from the 'inverse problem'. This refers to problem of estimating unknown model parameters, such as the neural location of activity in MEG, from the measured data, in this case the MEG sensor signals. The inverse problem has infinite solutions, as many models may equivalently predict the same observations. As such, additional contextual information must be specified. MEG source analysis often also involves forward modelling, which takes advantage of the assumption that some model parameters are known and fixed, such as the geometry of the head, head tissue conductivity, and sensor locations. These fixed parameters are then used to estimate the data, and can be altered until the model predictions best fit the observed data.

Two different approaches to source modelling have developed separately in MEG analysis: source localisation and source imaging. Source localisation approaches consider that brain activity at any time point is generated by only a few brain regions. This approach often involves dipole fitting, in which a limited number of neural sources are estimated and altered to minimise the difference between the model predictions and the observed data. Source imaging approaches instead focus on the distribution of all neural currents over the entire

brain volume. These models consist of distributions of elementary sources, whose locations and orientation are fixed, and the activity of these sources is estimated all at once.

Beamforming

A beamforming source analysis approach was used in Chapter 5 of this thesis. This is a scanning technique aimed at discriminating between signals originating from the location of interest from those generated elsewhere in the brain. Spatial filters are used to systematically sift through the brain space and evaluate how a predetermined source model fits the observed data by scanning every voxel of the brain volume. This is achieved by forming a grid across the entire brain space, and then using narrow-band spatial filters to evaluate the activity of each brain region across this grid, whilst activity from other brain regions is attenuated. The output of this technique is a distributed score map of activity across the brain. Computing a beamformer output for each location independently allow for multiple sources without making any assumption regarding the total number of neural sources of activity.

Strengths and limitations of MEG

MEG has advantages over both fMRI and EEG. fMRI signals reflect brain activity indirectly, by measuring the oxygenation of blood flowing near active neurons, whereas MEG signals are obtained directly from neuronal electrical activity, and provides timing as well as spatial information about brain activity. MEG does not make any operational noise, unlike fMRI, which can be extremely noisy. While fMRI measurement requires the complete absence of subject movement during recording, MEG measurement does not, so children can move their heads within the MEG helmet. Finally, MEG provides us with excellent temporal resolution of brain activation with sub-millisecond precision, whereas fMRI measurement provides poor temporal information. However, as MEG only measures activity on the surface

of the brain and can't distinguish activity from small areas, it doesn't give the full depth or spatial resolution of fMRI.

MEG also provides more accurate spatial localisation of neural activities than EEG, a complementary method of recording electrical brain activity. An advantage MEG has over EEG is that unlike electrical fields, magnetic fields travel virtually unaltered across the skull, meaning it's possible to more accurately measure where activity comes from. While EEG is strongly degraded by the heterogeneity in conductivity within head tissues (e.g., insulating skull vs. conducting scalp), this effect is extremely limited in MEG, resulting in greater spatial discrimination of neural contributions. However, EEG is sensitive to both tangential and radial components of a current source in a spherical volume conductor, whereas MEG detects only its tangential components. EEG can, therefore, detect activity both in the sulci and at the top of the cortical gyri, whereas MEG is most sensitive to activity originating in sulci. EEG is, therefore, sensitive to activity in more brain areas, but activity that is visible in MEG can also be localized with more accuracy.

References

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VAS scale ratings across groups

	AN-C (n=12)		AN-R (n=14)		HC (n=16)		Significance (p two tailed)	Pairwise post hoc group comparisons
VAS	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Happiness	50.8	27.4	57.2	26.2	74.1	17.7	.034	HC>AN-C
Despondence	31.8	27.7	27.4	22.2	19.8	20.5	.390	---
Anxiety	34.8	26.6	22.9	20.1	20.4	24.0	.260	---
Hunger	51.3	23.4	61.1	26.3	77.8	16.4	.010	HC<AN-C
Thirst	49.7	30.1	53.7	25.1	63.7	23.1	.339	---
Fullness	33.3	29.4	22.1	29.0	14.8	12.7	.147	---
Desire to eat	50.9	29.6	65.6	26.5	78.3	15.5	.018	HC<AN-C
Feelings of fatness	51.2	27.9	56.4	13.5	45.7	15.1	.321	---
Fear of fatness	78.8	19.5	55.9	25.3	32.3	20.0	<.001	AN-C>AN-R>HC

--- denotes non-significant