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**Brain-directed interventions for eating disorders:
The potential of repetitive transcranial magnetic stimulation in the treatment of
anorexia nervosa**

McClelland, Jessica Kate

Awarding institution:
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**Brain-directed interventions for eating disorders: the potential
of repetitive transcranial magnetic stimulation in the treatment
of anorexia nervosa.**

Jessica McClelland

Institute of Psychiatry, Psychology and Neuroscience, King's College London

Thesis submitted to King's College London for the degree of

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Abstract

Background: Advances in neuroscience have led to a deeper understanding of the neuro-circuitry associated with eating disorders (ED). There is however, a lack of brain-directed treatment options. Neuromodulatory techniques have therapeutic efficacy in other psychiatric disorders and evidence in ED is promising. There is a need for further studies of neuromodulation in ED, to probe disease mechanisms and to develop novel treatments. The aim of this research is to explore the use of neuromodulation in ED and specifically assess the utility of repetitive transcranial magnetic stimulation (rTMS) in anorexia nervosa (AN).

Methods: An overview of ED and their neurocircuitry underpinnings is presented. A systematic review of the literature regarding the effects of neuromodulation on eating related outcomes was also conducted. The effects of neuronavigated (MRI-guided) rTMS in AN is explored in a single-session randomised control trial (RCT) and in a 20-session therapeutic case series.

Results: The systematic review supports further research on neuromodulation in ED. The single-session RCT of real versus sham rTMS in 51 individuals with AN demonstrated that following real rTMS, individuals report reduced AN symptoms and an increased liking of specific foods. Real/sham rTMS did not alter salivary cortisol concentrations and levels of cortical excitability were associated with AN symptomatology. Lastly, rTMS proved to be safe, tolerable and acceptable in people with AN. A neurocognitive measure of intertemporal choice showed that rTMS encourages prudent decision making in AN: this may underlie the effects of rTMS on AN symptoms. Whilst a therapeutic case series of five individuals with enduring AN did not lead to weight gain, significant improvements in ED and general psychopathology were reported and sustained.

Conclusions: rTMS has the ability to improve core symptomatology in AN and alter decision making processes. Therefore, neuromodulation may be a viable treatment adjunct for people with an ED.

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I would like to dedicate this thesis to the most important people in my life. Dad and Jan thank you for being my number one supporters, for your love and generosity and for encouraging me to do something different – this thesis is as much mine as it is yours. Mum, thank you for your love, early sacrifices and for instilling in me your immense work ethic. Jamie, thank you for keeping a smile on my face throughout every single step of this journey – I could not have done this without you, you are amazing. Grandma and Grandpa, thank you for your endless support, you both mean the world to me. Tim and Kelly, thanks for being there and for keeping me involved with the kids. Finally, to the Rush, Fraser, Large & Dove family, thank you for making me feel so at home.

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Abbreviations used throughout the thesis

AN	anorexia nervosa
BDNF	brain derived neurotrophic factor
BED	binge eating disorder
BMI	body mass index
BN	bulimia nervosa
DASS-21	depression, anxiety and stress scale (21 item version)
DBS	deep brain stimulation
DLPFC	dorsolateral prefrontal cortex
DMPFC	dorsomedial prefrontal cortex
DSM	diagnostic and statistical manual of mental disorders
ED	eating disorder(s)
EDE(-Q)	eating disorder examination (-questionnaire)
EDNOS	eating disorder not otherwise specified
FCT	food challenge task
HF	high frequency
HS/HC/HP	healthy subjects/controls/participants
LF	low frequency
MRI	magnetic resonance imaging
PFC	prefrontal cortex
RCT	randomised control trial
rTMS	repetitive transcranial magnetic stimulation
SD	standard deviation
TMS	transcranial magnetic stimulation
TD/DD	temporal/delay discounting
tDCS	transcranial direct current stimulation
VAS	visual analogue scale
VNS	vagus nerve stimulation

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Papers associated with thesis

This paper forms the basis of Chapter 2:

McClelland, J., Bozhilova, N., Campbell, I.C. & Schmidt, U. (2013). A systematic review of the effects of neuromodulation on eating and body weight: evidence from human and animal studies. *European Eating Disorders Review*, 21 (6), 436-455 (A copy of this paper is included in Appendix A.1).

This paper forms the basis of Chapters 3 and 4:

McClelland, J., Kekic, M., Bozhilova, N., Nestler, S., Van Den Eynde, F., David, A., Rubia, K., Campbell, I.C. & Schmidt, U. (submitted). A randomized controlled trial of neuronavigated repetitive transcranial magnetic stimulation in anorexia nervosa.

These papers form the basis of Chapter 5:

McClelland, J., Bozhilova, N., Nestler, S., Campbell, I.C., Jacob, S., Johnson-Sabine, E. & Schmidt, U. (2013) Improvements in symptoms following neuronavigated repetitive transcranial magnetic stimulation in severe and enduring anorexia nervosa; findings from two case studies. *European Eating Disorders Review*, 21 (6), 500-506. (A copy of this paper is included in Appendix A.2).

McClelland, J., Kekic, M., Campbell, I.C. & Schmidt, U. (submitted). Therapeutic repetitive transcranial magnetic stimulation in five cases of enduring anorexia nervosa.

Conference and research presentations associated with thesis

Conference presentations:

McClelland, J. (2015, accepted) A randomised single-session sham-controlled trial of neuronavigated repetitive transcranial magnetic stimulation in anorexia nervosa. Oral presentation at the International Conference on Eating Disorders (ICED) in Boston, U.S.A.

McClelland, J. (2015, accepted) A therapeutic case series of neuronavigated repetitive transcranial magnetic stimulation in enduring anorexia nervosa. Oral presentation at the International Conference on Eating Disorders (ICED) in Boston, U.S.A.

McClelland, J. (2014) Neuromodulation in eating disorders: where we are and where we are going. Oral presentation at the Eating Disorders International Conference (EDIC) in London, U.K.

McClelland, J. (2013). A systematic review of the effects of neuromodulation on eating behaviour: Implications for brain directed treatments in eating disorders. Oral presentation at the Australia and New Zealand Academy for Eating Disorders (ANZAED) conference in Melbourne, Australia.

McClelland, J. (2012). Transcranial magnetic stimulation in eating disorders. Oral presentation at the European conference for eating disorders in Lyon, France.

Research presentations:

The research included within this thesis has been presented at departmental meetings at the Institute of Psychiatry, Psychology and Neuroscience, King's College London (chaired by Prof Ulrike Schmidt, Prof Janet Treasure and Prof Iain Campbell) and hospitals/clinical teams within London; e.g. the Phoenix Wing of St Ann's Hospital, Tottenham and Chase Farm Hospital, Enfield.

Declaration of candidate's role

Chapter 1: General introduction.

All work is the candidate's own.

Chapter 2: A systematic review of the effects of neuromodulation on eating and body weight; evidence from human and animal studies

The candidate was the main contributor to the development and process of the systematic review conducted on the potential of neuromodulation techniques for the treatment of ED. This work was done in close collaboration with an undergraduate student, Ms Natali Bozhilova who was on a one-year placement at the Section of Eating Disorders under the supervision of the candidate, Prof Schmidt and Prof Campbell.

Chapter 3: A randomised single-session sham-controlled trial of repetitive transcranial magnetic stimulation in anorexia nervosa

This study involved 51 people with AN. Recruitment, the administration of real/sham rTMS and data analysis was done by the candidate. The candidate was the main contributor to the data collection and data entry, in collaboration with Ms Natali Bozhilova. Due to the double blinded nature of the trial, three individuals were needed at each session – one to administer the rTMS (candidate), one to help with the rTMS neuronavigation equipment (primarily Mr Steffen Nestler) and one to do the pre- and post-assessments (primarily either Ms Natali Bozhilova or Ms Maria Kekic). Occasionally, other members of the Section of Eating Disorders assisted when the above-mentioned individuals were not available.

Chapter 4: The effects of repetitive transcranial magnetic stimulation on temporal discounting in anorexia nervosa

As the data for this study was collected within the RCT of Chapter 3, the role of the candidate is much the same as mentioned above. The administration of real/sham rTMS was done by the candidate, whilst the primary outcome – the administration of the temporal discounting (TD) task was done by the blinded researcher conducting the pre- and post-assessments (primarily Ms Natali Bozhilova or Ms Maria Kekic). Data entry and analysis was done by the candidate.

Chapter 5: A therapeutic case series of repetitive transcranial magnetic stimulation in five cases of enduring anorexia nervosa

This study involved the delivery of approximately twenty sessions of rTMS in five individuals with enduring forms of AN. Recruitment, data collection and analyses were done by the candidate. The candidate delivered all of the rTMS sessions and was assisted by one other person at each appointment. This was typically Ms Natali Bozhilova, Ms Maria Kekic or Mr Steffen Nestler.

Chapter 6: General overview.

All work is the candidate's own.

Chapter 1. General introduction

A recent initiative by The National Institute of Mental Health (NIMH) in the United States, the Research Domain Criteria, emphasises the importance of modern neuroscience tools in improving the diagnosis and treatment of psychiatric illnesses (Cuthbert, 2014; Insel et al., 2010). The growing understanding of eating disorders (ED) as brain-based mental illnesses supports the notion that research utilising neuroscience technologies will be of most use in elucidating the pathogenesis of disease and developing novel treatment approaches (Chavez & Insel, 2007; Schmidt & Campbell, 2013; van Elburg & Treasure, 2013).

This chapter summarises the history, diagnoses, epidemiology, pathogenesis, and current treatment approaches to ED. Following this, a summary of current neuroscience data is presented leading to a neurocircuit model of ED. Finally, common neuromodulation techniques with the ability to alter cortical activity are introduced to provide an understanding of their relevance and potential within ED.

Eating disorders: an overview

History

Cross-cultural descriptions of religious fasting, neurotic self-starvation and binge/purge behaviours date back to the medieval period (Bemporad, 1996; Keel & Klump, 2003; Miller & Pumariega, 2001). However, the first medically reported case of an ED was in 1689 when the physician Richard Morton described an 18-year old female with anorexic symptoms (Pearce, 2004). It was not until much later that Sir William Gull coined the term Anorexia Nervosa (AN) (Gull, 1874) and in 1979 that Prof. Gerald Russell first published a description of Bulimia Nervosa (BN) (Russell, 1979). By 1980 both AN and BN were diagnosable, psychiatric illnesses as defined in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM; A.P.A, 1980). Since then, ED have become widely researched and more thoroughly understood as serious, debilitating psychiatric disorders with a large degree of heterogeneity.

Diagnostic criteria

A number of diagnostic tools are employed in the classification, diagnosis and treatment of ED. The World Health Organisation's International Statistical Classification of Disease and Related Health Problems (ICD-10) is an established diagnostic tool (WHO, 1992). However, despite criticisms for its symptom-based categorisation (Insel, 2013), the DSM is the most extensively used nomenclature by clinicians and researchers for psychiatric diagnoses. In May 2013, almost a decade after the fourth edition (A.P.A., 1994), the DSM-5 was published and included a number of important changes to the diagnosis of three distinct ED¹ (A.P.A., 2013).

Characterised by significantly low weight and a disturbance in the perception of one's body, the diagnosis of AN was marginally revised in DSM-5. Most notably, given the growing understanding that amenorrhea (a previous criterion of AN) reflects nutritional state rather than illness severity and that this diagnostic requirement is irrelevant in men and for females taking oral contraception, amenorrhea was removed as a diagnostic criterion for AN in DSM-5 (Attia & Roberto, 2009). Additionally, rigid terminology relating to the overt *refusal* of weight maintenance, and *fear* of weight gain were clarified in the fifth edition of DSM. The two previously defined subtypes of AN, restricting and binge-eating/purging remain.

Binge-eating episodes, recurrent compensatory behaviours (e.g. self-induced vomiting) and an undue influence of body weight/shape on self-evaluation characterises BN. In DSM-5, the frequency of binge/purge behaviours required to meet BN diagnosis was reduced from twice weekly, to once a week over the past three months. Similarly, this lower binge frequency threshold was also applied to Binge Eating Disorder (BED), in which binge-eating causes marked distress however is not associated with inappropriate compensatory behaviours. In DSM-IV, BED was not a formal diagnosis; rather it was mentioned

¹ Four other DSM-5 feeding and ED categories are beyond the scope of this thesis; avoidant/restrictive food intake disorders, elimination disorder, pica and rumination disorder.

in the appendix as requiring further research. Recent evidence for the validity and clinical utility of BED (Wonderlich, Gordon, Mitchell, Crosby, & Engel, 2009) led to it being recognised as a separate diagnostic entity in DSM-5.

By relaxing the criteria of AN and BN, and including BED as a separate diagnosis, the DSM-5 aims to reduce numbers in the most common DSM-IV category, Eating Disorders Not Otherwise Specified (EDNOS; Call, Walsh, & Attia, 2013). Reportedly the diagnosis for up to 60% of ED cases (Fairburn & Bohn, 2005), EDNOS was renamed Other Specified Feeding or Eating Disorders (OSFED) in DSM-5 and incorporates a number of smaller sub-diagnoses (Fairweather-Schmidt & Wade, 2014). For example, OSFED includes conditions that do not meet full criteria of other ED such as atypical AN (weight within normal range), sub-threshold BN (binge eating and compensatory behaviours occur less than once a week), purging disorder (recurrent purging behaviours occur in the absence of bingeing) and night eating syndrome (regular episode of night eating). These sub-diagnoses are more homogeneous than EDNOS and aim to provide greater clinical utility. Importantly, the ED differ from other psychiatric disorders in that diagnoses are relatively unstable. Diagnostic flux is common, supporting the notion of shared underlying mechanisms and trans-diagnostic models of ED (Eddy et al., 2008; Milos, Spindler, Schnyder, & Fairburn, 2005).

Psychiatric comorbidity

ED rarely occur in isolation, commonly having other psychiatric comorbidities. Approximately 80% of ED sufferers have at least one other psychiatric comorbidity, with depression, anxiety and substance misuse the most common diagnoses (Braun, Sunday, & Halmi, 1994; Hudson, Hiripi, Pope, & Kessler, 2007; von Lojewski, Boyd, Abraham, & Russell, 2012). Additionally, personality disorders (Rosenvinge, Martinussen, & Ostensen, 2000) and developmental disorders such as autism and attention-deficit hyperactive disorder (ADHD) are more prevalent in individuals with ED (Bleck & DeBate, 2013; Huke, Turk, Saeidi, Kent, & Morgan, 2013; Råstam et al., 2013). Whether or not ED typically precede other psychiatric conditions or are in fact subsequent comorbidities themselves requires further clarification. Similarly, it is difficult to establish the

time of onset of co-morbid personality and developmental disorders when these conditions are assessed in people with an ED.

Epidemiology

The majority of existing ED epidemiological research is based on the DSM-IV criteria and therefore primarily investigates AN or BN. Although future research utilising DSM-5 will complicate comparisons to the existing literature, it should provide more accurate representations of the incidence and prevalence rates of ED, including those of BED and OSFED.

Incidence

The term *incidence* refers to the number of new cases in a population in a given year. In their review Hoek and van Hoeken (2003) suggest incidence rates of 8 and 12 cases per 100,000 persons per year for AN and BN respectively. More recent community studies report much higher incidence rates of AN and BN in adolescent groups (Smink, van Hoeken, & Hoek, 2012). Such community rates are typically much higher than those derived from medical settings, reflecting the large number of people who do not seek/or are unable to obtain treatment for their ED.

Whilst some suggest that the incidence of ED is increasing (Eagles, Johnston, Hunter, Lobban, & Millar, 1995; Keel & Klump, 2003) others report stable rates (Hoek & van Hoeken, 2003). Specifically, the incidence of AN seems to be stable since the 1970s and whilst BN increased threefold between 1988 to 1993, rates have fallen since (Currin, Schmidt, Treasure, & Jick, 2005; Turnbull, Ward, Treasure, Jick, & Derby, 1996). In comparison there has been a rise in the diagnoses of EDNOS (Micali, Hagberg, Petersen, & Treasure, 2013). The incidence of ED is highest amongst adolescents (Smink et al., 2012) and varies enormously between the genders (Currin et al., 2005).

Prevalence

The number of cases in a population at any given time is referred to as the *prevalence* of a disorder. The lifetime prevalence, that is the proportion of

people who have had an ED at any point in their life, for AN, BN and BED (based on the DSM-IV) are estimated at 0.9%, 1.5%, 3.5% for women and 0.3%, 0.5% and 2.0% for men respectively (Hudson et al., 2007). A more recent review reports similar rates ranging from 1.2-2.2% in AN and 1-2.9% for BN (Smink et al., 2012). Despite only recently being recognised as a separate diagnostic entity, BED is reportedly more common than both AN and BN (Hay, Mond, Buttner, & Darby, 2008).

Prognosis

Evidence suggests that the onset of an ED during adolescence has a better prognosis than in adulthood (Fisher, 2003; Goddard et al., 2013). There is currently insufficient data to assess long-term outcomes of both EDNOS and BED (Ben-Tovim et al., 2001; Berkman, Lohr, & Bulik, 2007) whilst remission rates of around 70% at up to 10 years follow-up have been reported in BN (Ben-Tovim et al., 2001; Keel, Mitchell, Miller, Davis, & Crow, 1999; Keski-Rahkonen et al., 2009). Outcomes for AN are the worst of the ED – less than half of sufferers recover, demonstrating either a full or partial ED at follow-up, whilst 20% remain chronically ill (Goddard et al., 2013; Keski-Rahkonen et al., 2007; Steinhausen, 2009; Steinhausen, 2002).

Mortality

All ED have elevated mortality risks, with AN suggested to have the highest mortality rate of all psychiatric illnesses (Arcelus, Mitchell, Wales, & Nielsen, 2011; Harris & Barraclough, 1998). In a longitudinal study, crude mortality rates of 4.0%, 3.9% and 5.2% were reported for AN, BN and EDNOS respectively. All-cause and suicide standardised mortality ratios (SMRs; ratio of observed to expected deaths) were also elevated across the ED and more so in BN and BED than had previously been reported (Crow et al., 2009). In comparison, a recent systematic review and meta-analysis identified overall SMRs of 5.86 for AN, 1.93 for BN and 1.92 for EDNOS (Arcelus et al., 2011). Mortality rates for the DSM-IV criteria EDNOS were identified as higher than those in AN by Crow et al. (2009) and equivalent to BN (Arcelus et al., 2011),

whilst a 12 year follow-up of inpatient BED patients yielded a mortality rate of 2.9% (Fichter, Quadflieg, & Hedlund, 2008).

Aetiopathogenesis

As has been outlined, ED are prevalent, serious and life-threatening illnesses. Significant attempts have been made to identify factors that contribute to the onset and maintenance of ED. In their seminal paper, Jacobi, Hayward, De Zwaan, Kraemer, and Agras (2004) identified gender, ethnicity, early eating/gastrointestinal problems, body image concerns and adverse experiences as risk factors for ED. Evidently, a number of factors from within a biopsychosocial framework are pertinent to the aetiopathogenesis of ED.

Psychological factors

Early explanations of ED were predominantly psychologically grounded. Initially, psychodynamic theories suggested ED to be a defence mechanism against sexual desires (Freud, 1961), a mother-centric objection to normal female development (Palazzoli, 1974) or an attempt to gain psychological independence and control (Bruch, 1974). Later, family-wide systemic theories were proposed (Minuchin et al., 1975), however they lacked complete empirical validation (Kog, Vertommen, & Vandereycken, 1987; Strober & Humphrey, 1987). More recently, research has diverged from familial theories of ED, and instead family collaboration is now seen as central in the successful treatment and recovery of ED in young people (Eisler, 1995).

Cognitive behavioural models of ED have also been proposed. Whilst Garner and Bemis (1982) suggest that the overvaluation of weight and shape is a central maintaining factor of ED, the need for control (Slade, 1982), extreme dietary restraint (Polivy & Herman, 1985) and escape from negative affect (Heatherton & Baumeister, 1991) have also been implicated. Fairburn, Shafran, and Cooper (1999) incorporated these concepts into a CBT model of AN and later into a trans-diagnostic approach (Fairburn, Cooper, & Shafran, 2003). More recently, Schmidt and Treasure (2006) proposed a cognitive-interpersonal maintenance model of AN that is not culture-bound by the undue influence of weight and

shape concerns. Within such models, personality factors such as perfectionism (Bastiani, Rao, Weltzin, & Kaye, 1995) and obsessive-compulsive traits in AN (Anderluh, Tchanturia, Rabe-Hesketh, & Treasure, 2003), and impulsivity (Claes, Vandereycken, & Vertommen, 2002) or sensation-seeking (Rossier, Bolognini, Plancherel, & Halfon, 2000) in BN and BED (Cassin & von Ranson, 2005) have also been proposed to drive ED.

Sociocultural factors

Despite being reported throughout medical history (Brumberg, 1988) and cross-culturally (Gordon, 2001; Keel & Klump, 2003) ED are often misconceived as a modern, sociocultural phenomenon. The ED cannot be explained by external factors alone, however a number of cultural, environmental and social factors have been proposed to contribute to their onset and maintenance.

Contemporary western culture explicitly promotes female thinness and a lean, muscular physique in males; furthermore research suggests that these ideals are becoming increasingly unrealistic and unattainable (Pope, Olivardia, Gruber, & Borowiecki, 1999; Spitzer, Henderson, & Zivian, 1999). Exposure to media images of such body ideals has been linked to body dissatisfaction and depression (see reviews Groesz, Levine, & Murnen, 2002; Hausenblas et al., 2013). Furthermore, groups of individuals where aesthetics and body weight is particularly important, such as dancers, gymnasts and models, and athletes in weight class sports such as rowing and boxing, demonstrate elevated body dissatisfaction and rates of ED (Arcelus, Witcomb, & Mitchell, 2014; Goltz, Stenzel, & Schneider, 2013).

Peer and parental relationships influence dieting behaviours, body dissatisfaction and ED related symptoms in adolescents (Arcelus et al., 2014). Similarly, Stice (2002) identified that a family or personal history of obesity, along with weight, shape or eating related criticisms are risk factors for BN. However, whilst such evidence for the potency of cultural body ideals, sport-specific pressures and social environments in the aetiopathogenesis of ED exist, they are dependent on interactions with individual psychological and biological traits.

Biological factors

The majority of biological research within ED has focused on the role of neurobiological dysfunctions (which will be discussed in depth later) and genetic predispositions. Familial aggregation and twin studies have contributed to understanding ED as complex, heritable and polygenic diseases (Jacobi et al., 2004; Trace, Baker, Penas-Lledo, & Bulik, 2013). Heritability estimates range from 22-74% and 52-83% for broad AN and BN respectively, and one study reports BED heritability as 57% (Bulik, Sullivan, Wade, & Kendler, 2000; Javaras et al., 2008). Additionally, higher rates of psychiatric disorders in relatives of ED probands when compared to healthy controls (HC) have been reported (Lilenfeld et al., 1998; Lilenfeld, Ringham, Kalarchian, & Marcus, 2008; Smith, Brandt, & Jimerson, 1989). Given that first-degree relatives and twins typically share genetic and environmental elements, and adoption studies in ED are scarce, differentiating between genetic and environmental factors is inherently difficult.

Two common approaches for elucidating genetic traits are pre-selecting a *candidate gene* based on evidence for its involvement in ED, and *genome-wide* screenings that aim to identify relevant genes with no priori hypotheses (see reviews Hinney & Volckmar, 2013; Jacobi et al., 2004; Trace, Baker, Peñas-Lledó, & Bulik, 2013). Candidate gene studies within ED have demonstrated the role of genes in serotonergic (Brewerton & Jimerson, 1996) and dopaminergic systems in AN (Bergen et al., 2005). The leptin gene has been implicated during weight fluctuations from acute to weight restored AN (Hebebrand et al., 1997), whilst brain derived neurotrophic factor (BDNF), essential for the growth and survival of neurones, has been implicated in restrictive AN (Ribasés et al., 2005). Also, early genome-wide association studies identified an association of chromosome 1 in AN (Grice et al., 2002). Whilst these associations have been recently confirmed across the spectrum of ED, studies remain underpowered to reach genome wide significance levels (Boraska et al., 2012; Boraska et al., 2014; Wade et al., 2013; Wang, Zhang, et al., 2011). Larger, international collaborations and meta-analyses are needed to overcome this (Boraska et al., 2014).

Gene-environment interactions and epigenetics

Environmental and biological mechanisms, such as those previously mentioned, interact and are therefore often inseparable, particularly in the case of psychiatry. The presence of certain genetic traits vulnerable to influences from specific environmental factors, otherwise known as gene x environment (G x E) interactions, may increase the risk of developing an ED. For example, Karwautz et al. (2011) suggest evidence for an interaction between several environmental factors and the serotonin transporter gene in AN. Furthermore, early physical environmental effects have the ability to alter genetic expression via epigenetic processes. Although research into epigenetic mechanisms within ED is scarce, interactions involving stress during pregnancy, perinatal complications and nutrition (both over and under feeding) have been proposed to alter the risk of ED related behaviours via epigenetic processes (Campbell, Mill, Uher, & Schmidt, 2011; Pjetri, Schmidt, Kas, & Campbell, 2012).

Current treatments

Given their complicated aetiopathogenesis, optimal treatment choices for ED, in particular for AN, remain largely undetermined. The current NICE (2004) guidelines recommend guided self-help (GSH) programs and cognitive behavioural therapy (CBT) for adults with BN and BED, family based therapy (FBT) for adolescent AN, yet there is still no treatment of choice for adult AN (NICE, 2004; Watson & Bulik, 2012). Whilst talking therapies have been the most widely researched and disseminated within the field of ED, there is also some suggested value in drug therapies (Tortorella, Fabrazzo, Monteleone, Steardo, & Monteleone, 2014). The efficacy of existing psychological and pharmacological interventions are discussed below.

Psychotherapy

Transdiagnostic treatment approaches for ED have been developed by Fairburn et al. (2009). These comprise of two forms of CBT which address ED specific psychopathology, and broader, general domains such as affect, perfectionism, low self esteem and interpersonal skills. At 15 months follow-up, a 53%

reduction in ED symptoms in EDNOS and BN patients was reported following this approach (Fairburn et al., 2009).

Other psychotherapies are designed for specific ED diagnoses. In adolescent BN, a more rapid reduction in bingeing behaviours occurred with CBT based GSH when compared to FBT (Schmidt et al., 2007) whilst FBT proved more effective than supportive psychotherapy (Le Grange, Crosby, Rathouz, & Leventhal, 2007). In the case of adult BN, GSH has proven efficacy and given its low cost, is recommended as a first-line treatment approach (Banasiak, Paxton, & Hay, 2005; Cooper, Coker, & Fleming, 1996). A number of studies have compared CBT to interpersonal therapy (IPT) and demonstrated a more rapid decrease in binge eating, vomiting and restraint and a greater chance of remission with CBT (Agras, Walsh, Fairburn, Wilson, & Kraemer, 2000; Fairburn et al., 1991). However, when comparing treatment approaches for BN at follow-up, CBT and IPT are equally effective (Hay, Bacaltchuk, Stefano, & Kashyap, 2009; Wilson, Grilo, & Vitousek, 2007). Moreover, CBT and IPT have similar efficacy in BED (Wilfley et al., 2002). Whilst an adapted form of CBT is recommended by NICE (2004) for BED, CBT based GSH has proved beneficial in BED and should also be considered as a first choice of treatment (Grilo & Masheb, 2005).

Family based interventions have the strongest evidence base for the successful treatment and long-term outcome of adolescent AN (Eisler, Simic, Russell, & Dare, 2007; Lock, 2011; Lock, Couturier, & Agras, 2006; Robin et al., 1999; Strober, Morrell, Burroughs, Salkin, & Jacobs, 1985). There is no gold-standard, first-line treatment for adult AN and only a small number of randomised control trials (RCT) have compared the efficacy of different psychotherapies with mixed findings. Specialised supportive clinical management (SSCM) is reportedly superior to both CBT and IPT (McIntosh et al., 2005). Whilst at 12 month follow-up psychodynamic therapy was advantageous to both enhanced CBT and treatment as usual (TAU), however enhanced CBT demonstrates quicker rates of weight gain and ED psychopathology improvements (Zipfel et al., 2014). Recently, indifference between SSCM to the Maudsley model of anorexia nervosa (MANTRA) have also been reported, however MANTRA is more acceptable than SSCM and works better in severe cases (Schmidt et al., 2012;

Schmidt et al., submitted). Similarly, SSCM and CBT-AN for severe and enduring AN have also been reported as similarly effective (Touyz et al., 2013).

Such varied results add to the difficulty in determining an optimal treatment for adult AN; there is little evidence that differentiates treatments such as CBT, focal psychodynamic, SSCM and MANTRA from one another. Whilst novel approaches such as cognitive remediation therapy (CRT) have been trialled, the evidence for their efficacy is mixed. In the only first-line study of CRT treatment for AN, CRT proved no more effective than CBT (Lock et al., 2013). Relapse prevention studies suggest that CRT alters neurocognitive outcomes (Brockmeyer, Ingernerf, et al., 2014), may be beneficial alongside TAU in severe/enduring AN (Dingemans et al., 2014), however is inferior to exposure based treatments (Steinglass et al., 2014). Therefore, the evidence for CRT is inconclusive and more data are required (Genders & Tchanturia, 2010; Tchanturia, Davies, & Campbell, 2007). Furthermore, evidence for the efficacy of both psychotherapy and pharmacotherapy in severe and enduring forms of AN is also significantly lacking and requires research (Andries, Frystyk, Flyvbjerg, & Stoving, 2014; Hay, Touyz, & Sud, 2012; Touyz et al., 2013).

Pharmacotherapy

Given the serious nature of ED, the limited efficacy of psychotherapy and the evidence for a neurobiological basis to ED, a number of drug therapies have been considered as treatment adjuncts. A recent review by Tortorella et al. (2014) considers the current data on pharmacological treatments for AN and BN. The efficacy of fluoxetine in reducing BN symptoms was demonstrated in nine out of twelve RCT, whilst tricyclic antidepressants, a range of monoamine oxidase inhibitors and the anticonvulsant topiramate also led to a reduction in symptoms when compared to placebo (Tortorella et al., 2014). In addition, topiramate lead to a reduction in binge frequency and BMI in obese individuals with BED (McElroy et al., 2003).

Research into drug therapies for AN is inconclusive – the efficacy of fluoxetine was not supported by Walsh et al. (2006), whilst the antipsychotic olanzapine lead to weight gain and/or reductions in ED psychopathology in four of seven

RCT (Tortorella et al., 2014). Similarly, a recent trial of dronabinol (a cannaboid agonist) versus placebo found small but significant weight gain in severe and enduring AN (Andries et al., 2014). Preliminary evidence for the use of the neuropeptide oxytocin in AN has also been considered and suggested as a future research avenue (Maguire, O'Dell, Touyz, & Russell, 2013).

Eating disorders and the brain

As is evident throughout the above overview, ED are multifaceted, difficult to treat, and often chronic mental illnesses. They can be conceptualised as biopsychosocial conditions and both researchers and clinicians should be aware of over simplistic approaches. Whilst psychosocial approaches have dominated the field to date, there has been a recent surge in biologically based ED research (Harris & Steele, 2014). This is likely to be a reflection of the wider understanding of ED as medical illnesses, the limitations of psychological approaches within such disorders and the on-going development of sophisticated neuroscience tools (e.g. functional neuroimaging), with the ability to delve deeper into neurobiological mechanisms. However, this rise in neurobiological-based ED research does not disregard earlier work; neuroscience has been informed by and can incorporate previous psychosocial findings, whilst non-biological approaches can benefit from recent advances in neuroscience. Interdisciplinary approaches involving clinicians and neuroscientists will enable a comprehensive understanding of the pathogenesis and effective treatment of ED (Holmes, Craske, & Graybiel, 2014) and thus, when considered within the wider framework, biological, brain-based empirical research in ED is crucial.

Although poorly understood, the role of the brain in the vulnerability, development and maintenance of ED is unquestionable. Whilst organic, brain-based differences may render an individual more susceptible to developing an ED, habit formation and the plasticity of the brain allow for seemingly external influences to become tangible. Along with a number of extensive and thorough reviews of the neuroscience data in ED to date (Frank, Bailer, Henry, Wagner, & Kaye, 2004; Jauregui-Lobera, 2012; Kaye, 2008; Kaye, Wierenga, Bailer,

Simmons, & Bischoff-Grethe, 2013; Lask & Frampton, 2011; Phillipou, Rossell, & Castle, 2014; Pietrini et al., 2011; Zhu et al., 2012), the following summary serves to provide a body of evidence for the brain-basis of ED.

Brain lesion cases

Uher and Treasure (2005) reviewed 54 cases of ED occurring in cases with brain lesions. They identified that hypothalamic lesions are the most common cause of AN-like symptoms, in particular weight loss, but rarely occur in conjunction with ED psychopathology. Whilst brainstem lesions have been associated with restrictive AN, this finding requires further substantiation. Interestingly, of eight cases presenting with ED psychopathology, four had frontal and temporal lesions, implicating the role of frontotemporal circuits. Similarly, complete remission of AN was demonstrated following the removal of a frontal brain lesion (Houy, Debono, Dechelotte, & Thibaut, 2007). More recently, ED related behaviours were reported following traumatic brain injury in four patients. Following temporal and hypothalamic lesions two patients presented with hyperphagia, whilst refusal of food or notable aversions to certain foods was associated with frontal lobe damage (Castano & Capdevila, 2010). Although the literature on brain lesions and ED is scarce, the role of the hypothalamus in changes to weight/appetite, and frontal regions in ED psychopathology is somewhat consistent.

Structural imaging

Nutritional deficiencies can have detrimental effects on brain structure. For example, lipids are essential for the myelination of neural axons, which enables fast conductivity for complex cognitive processes. A significant reduction in levels of adipose tissue i.e. during starvation has important consequences on brain composition and function. Research involving structural imaging techniques at both the acute and recovered stages of ED is vital in understanding neural links to clinical characteristics and brain-based ramifications of ED.

Computerised tomography (CT) produces three-dimensional x-ray images and has been used to investigate brain structure and volume in ED. Studies employing CT scans have demonstrated dilated ventricles, enlarged sulci and hemispheric fissures in both AN (Artmann, Grau, Adelmann, & Schleiffer, 1985; Kohlmeyer, Lehmkuhl, & Poutska, 1983) and BN (Kiriike et al., 1990; Krieg, Lauer, & Pirke, 1989). These findings reflect overall reductions in brain volume and cerebral atrophy during acute stages of illness, often irrespective of emaciation. Furthermore, such changes have been associated with impaired cognitive functions such as processing speed, concentration and reaction time (Kohlmeyer et al., 1983; Palazidou, Robinson, & Lishman, 1990). Fortunately, early CT data suggest that following recovery, these structural and cognitive changes are reversible (Artmann et al., 1985; Kohlmeyer et al., 1983; Krieg et al., 1989).

Compared to CT, structural magnetic resonance imaging (MRI) has less risk of radiation and enables higher resolution images. As such, MRI is now more widely used than CT and employs magnetic fields to produce images of biological tissues and fluids. Early studies of MRI in ED confirm previous CT findings of dilated ventricles, enlarged sulci and cerebral atrophy in AN (Kornreich et al., 1991) and BN (Hoffman et al., 1989). More recently, two systematic reviews assessed the use of voxel-based morphology in ED. Increased grey matter (GM) volume in frontal and ventral striatal areas was shown in BN, whilst the opposite, reductions in GM were identified in AN (Van den Eynde, Suda, et al., 2012). Similarly, a reduction in GM volume in brain areas implicated in reward and somatosensory processing in AN patients was reported soon after (Titova, Hjorth, Schiöth, & Brooks, 2013). Evidence for the normalisation of ventricular enlargement (Golden et al., 1996; Swayze et al., 1996) and white matter (WM) volume exists, however deficits in GM volume have been shown to either persist (Friederich et al., 2012; Katzman, Zipursky, Lambe, & Mikulis, 1997; Lambe, Katzman, Mikulis, Kennedy, & Zipursky, 1997; Roberto et al., 2011) or restore following weight restoration in AN (Lazaro et al., 2013; Mainz, Schulte-Ruther, Fink, Herpertz-Dahlmann, & Konrad, 2012).

Functional imaging

Whilst studying brain structure in an attempt to understand ED is important, the brain is a highly plastic, complex and interconnected organ. The development of a variety of neuroimaging techniques with the ability to examine the brain's electrical, neurobiological and haemodynamic activity has led to a greater understanding of the neural basis of ED.

Providing far higher temporal resolution than other forms of functional imaging, electroencephalography (EEG) enables a direct measure of neuronal electrical activity. Current EEG data in relation to ED suggest both sleep abnormalities, including increased awakening and wakefulness, and differences in event related potential in AN patients (see review Jauregui-Lobera, 2012). Such aberrations are most pronounced in underweight AN individuals, supporting the relationship between impaired nutritional state and EEG abnormalities. Whether or not these differences reduce with treatment and/or weight restoration remains controversial (Bradley et al., 1997; Crisp, Stonehill, & Fenton, 1971; Hatch et al., 2011). Examinations of neural activity in response to ED related stimuli have also been examined with EEG and findings are in accordance with those found with other neuroimaging modalities. For example, compared to obese women without BED, elevated frontal beta activity has been reported in response to food cues in obese women with BED. Moreover, beta activity was associated with eating related disinhibition and thus implicates the role of frontal activity in the sensitivity and response to salient cues in BED (Tammela et al., 2010). In response to such findings, the use of EEG neurofeedback has been suggested as a means of targeting these alterations in ED patients (Bartholdy, Musiat, Campbell, & Schmidt, 2013).

Positron emission tomography (PET) is a method of imaging designed to study the function of the brain via the relationship between energy consumption and neural activity. A PET image is created by injecting a radioactive isotope into the blood and it travelling to metabolically active areas of the brain. In PET ED research to date, studies have investigated alterations in regional cerebral

glucose metabolism (rCGM) along with the role of the monoamine neurotransmitters serotonin (5-hydroxytryptamine; 5-HT) and dopamine.

A body of PET literature investigating rCGM in ED exists. Hypermetabolism in the caudate nuclei (Delvenne, Goldman, De Maertelaer, & Lotstra, 1999; Delvenne et al., 1996; Herholz et al., 1987; Krieg, Holthoff, Schreiber, Pirke, & Herholz, 1991) and medial temporal regions (Gordon et al., 2001) has been found in AN. In contrast, global and regional hypometabolism, in particular throughout frontal and parietal areas, has also been reported in both AN and BN (Delvenne, Goldman, Biver, et al., 1997; Delvenne et al., 1999; Delvenne et al., 1996; Delvenne, Goldman, Simon, De Maertelaer, & Lotstra, 1997; Delvenne et al., 1995). Such rCGM alterations have been suggested to normalise after weight gain (Delvenne et al., 1996; Frank et al., 2007; Herholz et al., 1987).

Along with investigations into rCGM, PET studies have examined the role of serotonergic function in ED, focussing mainly on the binding receptors 5-HT_{1A} and 5-HT_{2A}. Increased binding potential of 5-HT_{1A} in both AN and BN (when compared to HC) has been reported (Bailer et al., 2007; Bailer et al., 2005; Galusca et al., 2008; Kaye, 2008; Tiihonen et al., 2004) whilst a reduction in binding of 5-HT_{2A} (Audenaert et al., 2003) has been shown to persist in both recovered AN (Bailer et al., 2004; Frank et al., 2002) and BN individuals (Kaye et al., 2001). Moreover, Bailer et al. (2007) report that ED subtypes can be distinguished via their differences in serotonin receptor activity.

Altered dopamine activity in ED has also been established via PET, demonstrating a reduction in striatal neurotransmission in both BN (Broft et al., 2012) and recovered AN (Frank et al., 2005). Furthermore, a direct relationship between the interaction of serotonin transporter and striatal dopamine activity has recently been associated with harm avoidance behaviours in both AN and BN (Bailer et al., 2013). Whilst the implications of these abnormalities in serotonergic and dopaminergic function are discussed later, it is likely that they contribute to a number of ED characteristics such as altered satiety signals, impulsivity abnormalities, diminished reward sensitivity and aversive food-motivation drives.

Single-photon emission computed tomography (SPECT) enables the visualisation of brain function by measuring the rate of regional cerebral blood flow (rCBF) through different areas of the brain. The interpretation of SPECT research relies on the premise that active brain areas require more oxygen and thus demonstrate increased rCBF. In part agreement with PET research, AN has been associated with hypoperfusion in frontal, parietal and temporal regions (Chowdhury et al., 2003; Gordon, Lask, Bryant-Waugh, Christie, & Timimi, 1997; Kuruoglu et al., 1998; Nozoe et al., 1995; Råstam et al., 2001; Takano et al., 2001) and areas including the anterior cingulate cortex (ACC; Naruo et al., 2001; Takano et al., 2001) and amygdala (Chowdhury et al., 2003). However, there is some evidence that BN is associated with frontotemporal hyperperfusion (Nozoe et al., 1995). Despite reported differences regarding whether or not rCBF alterations normalise (Frank et al., 2007; Kojima et al., 2005; Kuruoglu et al., 1998) or persist in recovered individuals (Frampton, Watkins, Gordon, & Lask, 2011), temporal hypoperfusion during the acute stages of an ED has been correlated with long-term outcome and may therefore have prognostic value (Jimenez-Bonilla et al., 2009).

Similarly to SPECT, functional MRI (fMRI) enables investigations into how different parts of the brain function and interact with each other. Since active brain areas require oxygen, as blood passes through functionally active brain tissue and oxygen levels are depleted, blood oxygen level detection (BOLD) signals can be used to identify networks of brain activity. Numerous fMRI studies have compared recovered and chronic ED patients to HC in their brain responses to salient stimuli (see Zhu et al., 2012 for a thorough review). When viewing foods images, individuals with ED demonstrate altered activation of limbic regions such as the insula and amygdala (Ellison et al., 1998; Holsen et al., 2012; Joos, Saum, van Elst, et al., 2011; Kim, Ku, Lee, Lee, & Jung, 2012). Moreover, prefrontal responses to food images have differentiated both AN and BN individuals from their healthy counterparts (Brooks et al., 2011; Joos, Saum, Zeeck, et al., 2011; Uher et al., 2004). Interestingly, when compared to both HC and currently ill individuals, recovered AN individuals demonstrate heightened neural responses to both rewarding and aversive food stimuli (Cowdrey, Park,

Harmer, & McCabe, 2011) and persisting hyperactivity of the ACC and medial prefrontal cortex (MPFC) (Uher et al., 2003). These findings are incorporated and explored within the succeeding neurocircuit model of ED; involving the over-representation of limbic responses (i.e. diminished reward sensitivity and/or heightened emotional responses) in conjunction with impaired and/or exaggerated cognitive control.

Response to food images during satiated and hungry states has also been examined in order to understand state related effects on neural networks. Increased activation to high-calorie foods in areas such as the amygdala and insula has been demonstrated in fasted HC (Gizewski et al., 2010; Goldstone et al., 2009). In contrast, both weight-restored and currently ill AN samples showed hypoactivations when fasted, which persist in the insula of satiated, acute AN individuals (Holsen et al., 2012; Santel, Baving, Krauel, Munte, & Rotte, 2006). These findings highlight limbic activation differences between AN and HC in response to ED salient stimuli, as well as the importance of considering state related neural effects. Similarly, supporting the notion that food reactivity is modulated by internal motivational states Uher, Treasure, Heining, Brammer, and Campbell (2006) also identified heightened reactions to fasting in females, providing a neural basis to the gender-related susceptibility to ED.

More recently Van den Eynde, Giampietro, et al. (2013) suggest that BN individuals do not differ from HC in their processing of food related images, however, when comparing their own bodies to slim ideals, people with BN engage limbic structures (in particular the insula) less than their healthy counterparts. Similarly, women with ED demonstrate reduced activity in the insula and aversive responses (e.g. heightened anxiety) when viewing images of themselves (Sachdev, Mondraty, Wen, & Gulliford, 2008). Likewise, reduced activation of the lateral fusiform gyrus and parietal cortex in response to line drawings of female bodies (Uher, Murphy, et al., 2005), and the right fusiform gyrus and MPFC when engaging in body checking actions (Suda et al., 2013) differentiates people with ED from HC. In contrast, Friederich et al. (2010) demonstrated insula hyperactivity during body comparisons and others suggest that the neural correlates of two distinct body image components (attitudes

towards one's body and body size estimation) can be identified in both AN and BN (Mohr et al., 2011; Mohr et al., 2010). These findings implicate brain regions central to somatosensory processing and may account for the characteristic body image disturbance and dissatisfaction apparent within ED.

Arguably a more potent and realistic method of symptom provocation, the administration of food substances during fMRI have been investigated in a small number of ED studies. Research involving the administration of glucose/sucrose in both recovered AN and BN has demonstrated reduced neural activation (compared to HC) in areas including the insula (Wagner, Aizenstein, et al., 2008) and ACC (Frank et al., 2006). Furthermore, the receipt of chocolate milkshake in BN was associated with hypoactivation of the insula (Bohon & Stice, 2011). More recently the neural effects of sucrose were found to be different in AN and BN having significantly diminished and elevated insula activation responses respectively (Oberndorfer et al., 2013). In general, this evidence for diminished reward sensitivity is thought to reduce the palatable and hedonic nature of food for ED patients, potentially contributing to the reduced motivation to eat in AN, and the need to binge eat to achieve satiety in BN.

Along with using symptom provocation tasks, the administration of neuropsychological assessments whilst undergoing fMRI has proven useful in exploring the neurocognitive profile of ED. It is well documented that the ED are associated with a number of neuropsychological traits including cognitive inflexibility (Tchanturia et al., 2012), altered sensitivity to rewards (Harrison, O'Brien, Lopez, & Treasure, 2010) and disturbances in impulsivity (Rosval et al., 2006). fMRI studies have produced data on the potential neural correlates of these characteristics. For example, impaired behavioural response shifting in AN has been associated with hypoactivation in the thalamus, ventral striatum, ACC and cerebellum in conjunction with predominant frontoparietal activation (Zastrow et al., 2009). Moreover, tempoparietal hyperactivation has been associated with working memory tasks in acute AN which returned to normal following treatment (Castro-Fornieles et al., 2010). Interestingly, during an ED salient Stroop task, thin and fat words were associated with hypoactivation of limbic structures and prefrontal cortex (PFC) dominance respectively

(Redgrave et al., 2008). This finding further supports the notion of reduced limbic processing of 'rewarding' cues and the over-activation of cognitive control circuits in response to aversive cues. Others also suggest a deficiency in the processing of positive and negative valence in the anterior ventral striatum in both AN and BN (Wagner et al., 2010; Wagner et al., 2007). Such findings indicate difficulties in identifying the emotional significance of stimuli across the ED. Moreover, a failure to engage frontal-striatal networks has been associated with reward processing in BED patients (Balodis et al., 2014), implicit learning in sub-threshold BN (Celone, Thompson-Brenner, Ross, Pratt, & Stern, 2011) and inhibitory control in both AN and BN (Lock, Garrett, Beenhakker, & Reiss, 2011; Marsh et al., 2011; Marsh, Steinglass, et al., 2009; Oberndorfer, Kaye, Simmons, Strigo, & Matthews, 2011). These findings suggest shared disturbances in the processing of emotional salience, reward and inhibitory control.

More recently, fMRI studies of resting state functional connectivity, i.e. neural activity in the absence of cue or task administration, have been conducted. Such investigations allow for an examination of the default mode network (DMN), which is typically more active at rest than during attention-demanding tasks (Park, Godier, & Cowdrey, 2014). Compared to controls, individuals recovered from AN demonstrate increased temporal coherence (i.e. spontaneous coactivation) in the DMN, and between the DMN and areas such as the dorsolateral prefrontal cortex (DLPFC) (Cowdrey, Filippini, Park, Smith, & McCabe, 2014). Similarly, individuals with acute AN (compared to controls) demonstrate increased functional connectivity within areas of the fronto-parietal network and in the anterior insula which is associated with poor interoceptive awareness (Boehm et al., 2014). These abnormalities in resting state networks suggest dysfunction in self-referential and cognitive control processes and further support the notion of altered neural circuitry underpinnings to ED.

The neurocircuitry of eating disorders

As has been outlined, numerous brain regions have been implicated in the aetiology and symptomatology of ED. Drawing on such evidence, a number of conceptual, neuroscience-based models of ED have been proposed. Neurodevelopmental models of ED have been suggested (Connan, Campbell, Katzman, Lightman, & Treasure, 2003; Southgate, Tchanturia, & Treasure, 2005) along with cognitive neuroscience AN-specific models centered around learning and habit formation (Steinglass & Walsh, 2006) or the pronounced role of the insula (Nunn, Frampton, Gordon, & Lask, 2008). Whilst these models identify fundamental neural substrates and cognitive processes in the development of ED, recent neurocircuit models provide more comprehensive accounts of the important functional and effective connectivity between cortical and subcortical regions (Friederich, Wu, Simon, & Herzog, 2013; Hatch et al., 2010; Kaye, Fudge, & Paulus, 2009; Kaye, Wagner, Fudge, & Paulus, 2011; Kaye et al., 2013; Lipsman, Woodside, & Lozano, 2014; Marsh, Maia, & Peterson, 2009). Such existing hypotheses of ED have informed and been incorporated within the following model and rationale to this thesis.

Neurocircuitry and self-regulation in eating disorders

As has been discussed previously, the ED are biopsychosocial disorders, arising from a combination of predisposing biological, psychological and personality factors, modified by epigenetic processes and exacerbated by potent sociocultural pressures. These factors are particularly pertinent during adolescence, a time of hormonal fluctuations, brain developmental changes and a heightened need for social acceptance. Furthermore, adolescence is a key period in the maturation of important neural circuitry and the subsequent development of self-regulation abilities (Marsh, Maia, et al., 2009).

Affective regulation

Adequate development of neural circuitry is central to the effective regulation of emotional responses. Firstly, the ventral circuit, including the amygdala, nucleus accumbens and insula, is important in the identification and coding of

emotionally salient stimuli. Secondly, the dorsal circuit, incorporating areas such as the PFC, parietal regions and the cingulate cortex, is responsible for responding to ventral signals via cognitive control/executive functions such as decision making, selective attention, planning and modulating emotional responses (Ochsner & Gross, 2007; Phillips, Drevets, Rauch, & Lane, 2003). These and other models of emotion regulation propose that 'bottom-up' emotion generation arises from subcortical, limbic neural structures whilst dorsal, prefrontal regions exert 'top-down' cognitive control.

Disturbances within such circuitry are proposed to underlie emotion dysregulation across various psychiatric disorders (Ochsner, 2008; Phillips, Ladouceur, & Drevets, 2008). Specifically, in relation to ED, key components of the neural circuitry proposed to underlie emotion dysregulation models have been implicated in neuroimaging data (see Figure 1.1). Moreover, emotion dysregulation and alexithymia is well documented across the spectrum of ED (Brockmeyer, Skunde, et al., 2014; Gilboa-Schechtman, Avnon, Zubery, & Jeczmien) and therefore, alterations in the neural networks that subserve emotion and mood regulation are highly pertinent to ED.

Appetite regulation

Similar components of the neural circuitry proposed to be involved in emotion regulation difficulties are also implicated in appetite disturbance. For example, a recent study found that modulation of the amygdala lead to loss of appetite in rats (Cai, Haubensak, Anthony, & Anderson, 2014) and such ventral circuit structures are proposed to play a key role in the hedonic aspects of eating such as pleasure and motivation (Koh, Wilkins, & Bernstein, 2003). Thus, the well-documented alterations in mesolimbic activity in ED sufferers is likely to contribute to the heightened emotionality and/or diminished motivation towards food and eating. In response, dorsal circuitry is engaged during decisions regarding the approach or avoidance of food and aberrant activity may be an attempt to reduce dysphoric mood (e.g. heightened fear/anxiety) (Kaye et al., 2009; Kaye et al., 2011). Therefore, the integrated nature of the

neurocircuitry underling affect and appetite control is highly relevant to the manifestation of self-regulatory control difficulties seen in ED.

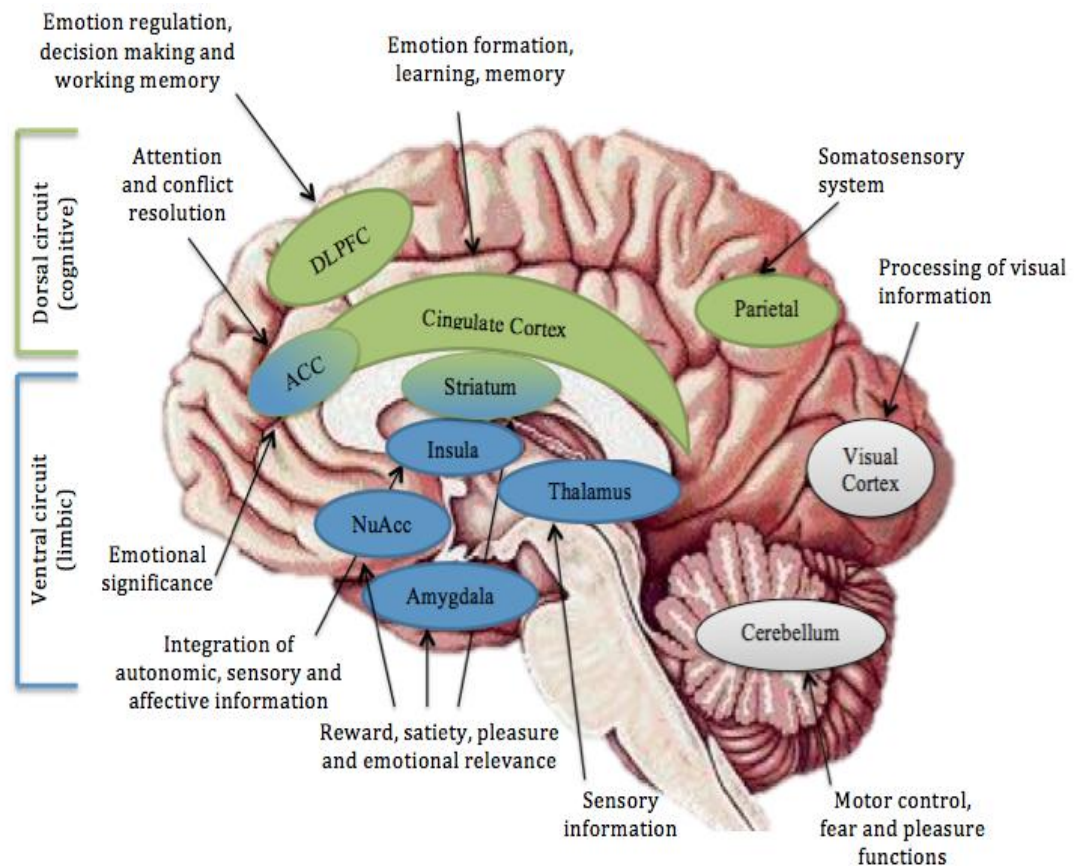


Figure 1.1 Brain areas implicated in eating disorders

The ventral/limbic circuit, including areas such as the insula, nucleus accumbens (NuAcc), amygdala and anterior cingulate cortex (ACC), is important in the identification and coding of emotional salience and therefore responsible for generating 'bottom-up' emotional responses. The dorsal/cognitive circuitry, including areas such as the dorsolateral prefrontal cortex (DLPFC) and parietal regions, is engaged in response to such emotive signals and modulates executive functions (e.g. decision making) and 'top-down' cognitive control.

Self-regulatory control

In response to emotion dysregulation and appetite disturbances, fronto-striatal circuitry has also been suggested as a unanimous neural substrate of the self-regulatory control difficulties seen in ED (Brooks, Rask-Andersen, Benedict, & Schioth, 2012; Marsh, Maia, et al., 2009). For example, disturbances in the neural circuitry that regulate reward sensitivity and inhibitory control are

central to BN. Directional differences of reward circuitry activity in BN differs between studies (Brooks et al., 2011; Kim et al., 2012; Oberndorfer et al., 2013) however, evidence suggests that the hypoactivity of mesolimbic circuitry underlies diminished responsiveness to the palatable nature of food (Bohon & Stice, 2011; Frank, Reynolds, Shott, & O'Reilly, 2011; Frank et al., 2006). Moreover, a reduction in striatal dopamine neurotransmission further supports the notion of impaired mesolimbic circuitry in BN (Broft et al., 2012) and binge-eating behaviour may be an attempt to compensate for this diminished reward sensitivity.

The concurrent failure to engage frontal, cognitive control areas when presented with relevant stimuli (Joos, Saum, Zeeck, et al., 2011; Uher et al., 2004) and during inhibitory control tasks (Balodis et al., 2014; Lock et al., 2011) may underlie the impulsive traits of BN. This diminished cognitive control, coupled with the over-evaluation of weight and shape may underlie the binge and purging behaviours characteristic of BN. Interestingly, preliminary evidence suggests opposite brain activation patterns in BED. Specifically, enhanced reward sensitivity and medial orbitofrontal PFC activity (Schienle, Schafer, Hermann, & Vaitl, 2009) coupled with increased striatal dopamine levels (Wang, Geliebter, et al., 2011) have been found in BED. These findings suggest that compared to the diminished reward sensitivity and impaired cognitive control of BN, BED may be characterised on a neural level by heightened anticipatory reward.

Mesolimbic structures critical to affect regulation and nutritional homeostasis have long been implicated in the aetiology of AN (Lipsman et al., 2014; Nunn et al., 2008). Similarly to BN, the exact direction of altered mesolimbic activity requires further substantiation, however Friederich et al. (2013) suggest a combined over-representation of reward and fear related neural circuitry in AN. For example, hyperactivity in limbic areas such as the insula in response to symptom provocation (Cowdrey et al., 2011) may represent enhanced aversive motivation, whilst diminished responses may demonstrate impaired processing of the hedonic nature of food (Oberndorfer et al., 2013). Concurrent hyperactivity of the amygdala (Ellison et al., 1998; Joos, Saum, van Elst, et al.,

2011), a central structure in the formation of fear responses, is likely to contribute to the heightened food related anxiety experienced in AN and the consolidation of learned fear responses. Moreover, diminished dopaminergic drives in recovered AN (Frank et al., 2005) suggest a trait related disturbance in reward circuitry, whilst altered serotonergic activity may explain altered satiety signals, heightened aversive arousal and harm avoidance strategies such as food restriction (Bailer et al., 2013; Friederich et al., 2013).

In response to over-represented mesolimbic drives, exaggerated frontal activity (Brooks et al., 2011; Uher et al., 2003; Zhu et al., 2012) may facilitate the pathological rigidity and self-control typical of AN. This trait is demonstrated in the unique ability of individuals with AN to resist immediate gratification in favour of later, more desirable rewards i.e. food restriction in the pursuit of weight loss (Steinglass et al., 2012). Furthermore, predominant fronto-parietal activity has been associated with poor cognitive flexibility in AN (Zastrow et al., 2009). Such heightened PFC activity during cognitive control tasks and food exposure (Brooks et al., 2011; Uher et al., 2003) is thought to reflect dominant top-down processing in an attempt to modulate aberrant mesolimbic signals and resulting dysphoric mood. Moreover, alterations in the resting functional connectivity of interoceptive and cognitive control networks have been demonstrated in AN and support the notion of impaired neural circuitry (Boehm et al., 2014; Cowdrey et al., 2014).

Symptom/diagnostic commonalities

Whilst evidence for ED subtype-specific neural activation patterns exist, Brooks et al. (2012) suggest that commonalities represent trans-diagnostic sporadic dominance of either top-down or bottom-up processing. Moreover, in the context of variable environmental challenges, temperamental dominance is suggested to dictate ED phenotype. In response to heightened fear and anxiety responses, dominant cognitive activity and therefore heightened self-regulatory control typifies restrictive AN, whilst impaired dorsal circuitry in response to diminished reward sensitivity and mood instability manifests in the poor inhibitory control symptoms of BN. Importantly, intermittent dominance of the

opposite system may often occur and thus account for symptom or diagnostic flux within ED (Brooks et al., 2012).

Chronicity

These neural network based disturbances that manifest in altered emotionality, appetite drives and self-regulatory control symptoms are then further maintained by the biopsychosocial factors that instigated them, positive reinforcement, temporary emotional respite and the consolidation of ED related coping mechanisms. With repetition, these conscious behaviours become ritualised, automatic and often compulsive habits that are increasingly difficult to unlearn and resistant to change (Godier & Park, 2014; Park et al., 2014; Steinglass & Walsh, 2006). This shift from active behaviours, to habitual and/or compulsive responses relies on neuroplasticity, the brain's ability to change in response to environmental stimuli and learning processes. Neuroplasticity has been implicated in other impulse control disorders (Muresanu, Stan, & Buzoianu, 2012) and may explain the deep-rooted and treatment resistant nature of ED with increasing illness duration. This model suggests that unless identified early, before the brain adapts to maladaptive behaviours, ED may require brain-directed treatment adjuncts in an attempt to restore underlying dysfunctional neurocircuitry and alleviate symptomatology.

The neurocircuit approach to ED outlined emphasises the importance of considering ED within a biopsychosocial framework. The neurodevelopmental role of altered fronto-striatal circuitry is central to explaining the self-regulation difficulties such as emotional processing, appetite disturbances and inhibitory control aberrations found in ED. The manifestation of these neural alterations into the phenotypic ED subtypes is explored, whilst commonalities and symptom/diagnosis crossover are also accounted for. Finally, the neural basis of learning and habit formation is the last, yet significant stage of this model, explaining how ED can become ingrained on a neural level and develop into chronic, treatment-resistant and life-threatening illnesses. This proposed model of dysfunctional neurocircuitry and resulting self-regulation difficulties in ED is schematically presented in Figure 1.2.

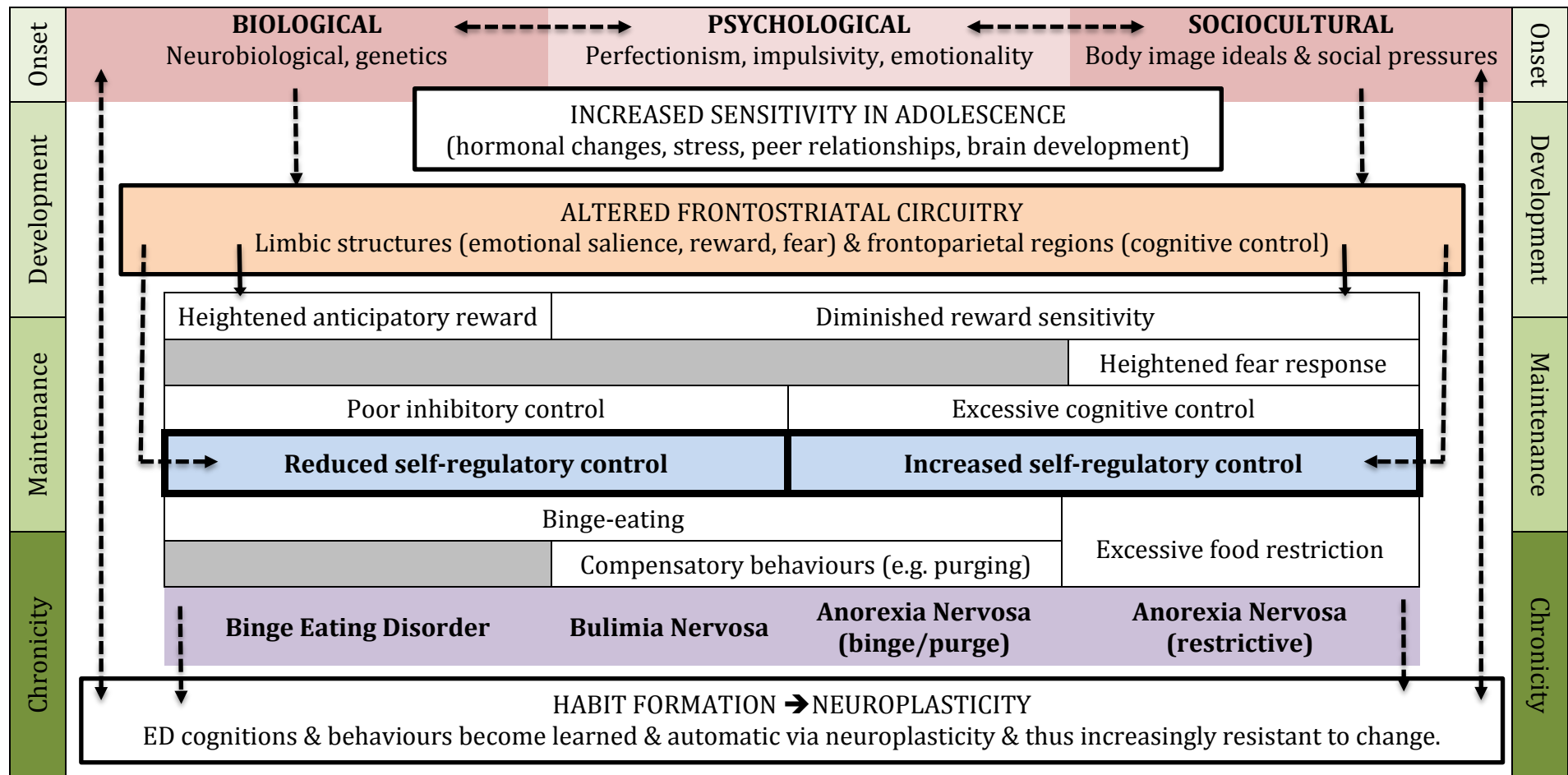


Figure 1.2 A schematic representation of the underlying neurocircuitry of self-regulation difficulties and resulting phenotypic behaviours in eating disorders

Neuromodulation techniques

On the basis of extensive neuroimaging literature, comprehensive neurobiological models and the limited efficacy of existing therapies, there is an indisputable need for novel, brain-directed treatment adjuncts to ED. This is further supported by the NIMH recognition of ED as brain based mental disorders and the subsequent development of the Research Domain Criteria (Chavez & Insel, 2007; Insel et al., 2010). Significant scope exists for investigations into neuromodulation techniques, which have the ability to directly, focally and implicitly influence the cortical and sub-cortical processes proposed to underlie ED. Therefore, neuromodulation techniques offer potential in probing disease mechanisms and exploring novel treatments for ED.

Four common neuromodulation techniques are relevant to this thesis, in particular the subsequent review (Chapter 2). They range from relatively non-invasive procedures, such as Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS), to more invasive procedures requiring surgery, such as Vagus Nerve Stimulation (VNS) and Deep Brain Stimulation (DBS). Such techniques are advantageous compared to older brain directed treatment approaches, such as Electroconvulsive Therapy (ECT), as they are non-lesional, adjustable and most are without severe side effects. Those investigated most widely and relevant to this thesis are summarised in Table 1.1.

Table 1.1 Common neuromodulation techniques

Type	Mechanism of action
Transcranial Magnetic Stimulation (TMS)	Electromagnetic induction modulates neural activity in the underlying cortex.
Transcranial Direct Current Stimulation (tDCS)	Weak current alters neuronal excitability. Neural effects depend on direction of current.
Vagus Nerve Stimulation (VNS)	Electrical stimulation of vagus nerve conveyed to other areas of the brain.
Deep Brain Stimulation (DBS)	Electrical pulses delivered to specific brain area central to symptom/condition.

Repetitive transcranial magnetic stimulation

TMS works on the principle of electromagnetic induction – the electrical current that is run through a TMS coil produces a magnetic field that can induce a secondary current in a nearby conductor. When a TMS coil is held up against the head, the electromagnetic field modulates neural activity in the underlying cerebral cortex. Initially, single pulse TMS was developed in order to investigate and demonstrate motor cortex excitability (Barker, Jalinous, & Freeston, 1985). However, the development of the ability to deliver of multiple pulses over a short period of time, known as repetitive TMS (rTMS), enabled longer lasting neural effects and investigations into behavioural and psychological conditions. When applied at a low frequency (LF; < 5Hz), rTMS suppresses cortical activity, whilst high frequency rTMS (HF; 5Hz or above) enhances cortical activity (Rossi, Hallett, Rossini, & Pascual-Leone, 2009; Rossini et al., 1994). Recent evidence suggests that HF rTMS applied to the left DLPFC has therapeutic efficacy in depression (Gaynes et al., 2014). As such, rTMS is approved by the Food and Drug Administration (FDA) in the United States as a second-line treatment for depression.

Transcranial direct current stimulation

tDCS applies a weak direct current from one electrode (excitatory; anode) to another (inhibitory; cathode). In comparison to rTMS, the mechanism by which tDCS works enables multiple stimulation designs; switching the position of the electrodes enables alternating excitation/inhibition between the right and left hemispheres. In comparison to rTMS, tDCS is safer, cheaper and easier to administer, however has not yet been as widely investigated. However, interest in tDCS is growing, having shown promising therapeutic effects in both Parkinson's Disease (Benninger et al., 2010; Boggio et al., 2006; Fregni et al., 2006) and Alzheimer's disease (Ferrucci et al., 2008) and more recently, in major depression (Ferrucci et al., 2009; Kalu, Sexton, Loo, & Ebmeier, 2012; Loo et al., 2012; Loo et al., 2010; Nitsche, Boggio, Fregni, & Pascual-Leone, 2009).

Vagus nerve stimulation

VNS involves the implantation of a stimulator device; the generator is placed under the clavicle in the chest and is connected to electrodes wrapped around the vagus nerve (Connor, Nixon, Nanda, & Guthikonda, 2012; Meneses et al., 2013). The vagus nerve, one of 12 cranial nerves, relays information to and from the brain to major organs including the heart, stomach and lungs. Electrical stimulation via VNS results in activation/inhibition of brainstem structures, which is then conveyed to other areas of the brain including the thalamus, frontal cortex, hypothalamus and limbic lobe (Chae et al., 2003). The use of VNS is FDA approved for the treatment of intractable epilepsy and depression, yet its therapeutic efficacy in depression is argued to require further substantiation in high quality controlled trials (Martin & Martin-Sanchez, 2012).

Deep brain stimulation

Finally, DBS is a technique that has been used for more than 25 years to modulate dysfunctional neurocircuitry. It involves the implantation of electrodes in a defined brain target deemed to be central to the clinical problem. Similarly to VNS, the electrodes are connected to a generator implanted in the body, which sends electrical pulses to the region of interest. Marked improvements in the major motor symptoms of Parkinson's disease have been found after DBS typically of either the globus pallidus, sub-thalamic nucleus or other thalamic targets (DeLong & Wichmann, 2012). Use of DBS now extends into psychiatric disorders for which there are neural based aetiological models. For example, promising therapeutic effects have been reported following DBS of the subgenual cingulate gyrus or the ventral internal capsule/ventral striatum in major depression (Taghva, Malone, & Rezai, 2012), the nucleus accumbens in obsessive compulsive disorder (de Koning et al., 2013; Greenberg et al., 2006) and the hypothalamus in Alzheimer's Disease (Laxton et al., 2010).

Summary

ED are complex, prevalent and debilitating mental disorders. Research has significantly advanced our understanding of their aetiopathogenesis and aided the development of important psychosocial and pharmacological interventions. However, remission rates remain unsatisfactory. Given the increasing volume of neuroscience data and resulting brain-based aetiological models, the utilisation of modern and sophisticated neuroscience tools, such as neuromodulation, will be of use in elucidating the neural basis of ED and for developing brain-directed treatment adjuncts to existing therapies.

Aims and hypotheses

The aim of this research was to investigate the potential of neuromodulation techniques in the treatment of ED, focusing specifically on the effects of rTMS in AN. Four major hypotheses were tested:

Hypothesis 1. Existing literature demonstrates that in human and animal populations, neuromodulation techniques have the ability to alter feeding and eating behaviour, body weight and ED related symptoms, and therefore have potential in the treatment of ED (Chapter 2).

Hypothesis 2. In patients with AN, core symptoms of AN will be reduced immediately and 24 hours after a single-session of real (as opposed to sham/placebo) HF rTMS to the left DLPFC (Chapter 3).

Hypothesis 3. Excessive cognitive control in AN will be reduced following real (as opposed to sham/placebo) HF rTMS to the left DLPFC (Chapter 4).

Hypothesis 4. In patients with enduring AN, ED and related psychopathology (e.g. mood) and weight will be improved immediately following therapeutic (20 sessions) HF rTMS to the left DLPFC and at follow-up, up to 6 months later (Chapter 5).

Thesis map

This thesis examines the potential of neuromodulation techniques for the treatment of ED. Specifically it focuses on an examination of the effects of rTMS in AN.

Chapter 1: Introduction

This chapter provides the background and rationale for this research. A summary of the existing research on the diagnosis, severity and treatment options for ED is provided. Relevant neuroscience data are presented, the neurocircuitry associated with ED is discussed and existing neuromodulation techniques are introduced.

Chapter 2: A systematic review of the effects of neuromodulation on eating and body weight; evidence from human and animal studies

A systematic review of the literature on neuromodulation techniques in relation to ED symptoms, eating/feeding behaviours and body weight examines the literature in this field. Evidence is assessed in relation to the potential use of neuromodulation for the treatment of ED.

Chapter 3: A randomised single-session sham-controlled trial of repetitive transcranial magnetic stimulation in anorexia nervosa

This chapter includes an in depth introduction to rTMS as a technique, together with a detailed description of the methods and design of the single-session, real versus sham rTMS, RCT that was conducted. The rationale and findings regarding the effects of HF rTMS to the left DLPFC on symptoms of AN are reported followed by data on its effects on food preferences and consumption. The effects of rTMS on stress levels (salivary cortisol) in AN are then presented and data on cortical excitability, the safety, tolerability and acceptability of rTMS in AN are reported. In each of the relevant sections, there is a discussion of the findings and their implications.

Chapter 4: The effects of repetitive transcranial magnetic stimulation on temporal discounting in anorexia nervosa

In this chapter, an introduction to the concept of temporal discounting (TD; the preference to choose smaller, immediate over larger later rewards) is presented and its association with choice impulsivity/controlled decision making is discussed. Literature on the use of TD tasks in relation to disordered eating and the effects of neuromodulation on TD is also reviewed. Using the same AN sample and RCT design described in Chapter 3, the results of the effects of rTMS on TD behaviour in AN are presented. These findings and their implications are discussed.

Chapter 5: A therapeutic case series of repetitive transcranial magnetic stimulation in enduring anorexia nervosa

A case series of five individuals with enduring AN treated with ~20 sessions of rTMS is presented. Within session data regarding ED experiences pre and post each rTMS session are then presented. One and six month follow-up data on weight, ED and general psychopathology are reported. Finally, qualitative information from both the participants and a third-party/significant other is presented. The results of these five cases are discussed together with the implications for the use of rTMS in the treatment of AN.

Chapter 6: General discussion

In this final chapter, the main findings are summarised in light of the strengths and weaknesses of this research. Directions for future research are suggested combined with a discussion of the clinical significance of this work.

**Chapter 2. A systematic review of the effects of
neuromodulation on eating and body weight; evidence from
human and animal studies**

Introduction

The ED are serious illnesses with often devastating consequences. Various forms of psychotherapy, often alongside medication, are currently the only treatment options available. Although these treatments work for some, dropout and relapse rates are high and a significant number of people do not respond to any of the treatment options currently available (Dejong, Broadbent, & Schmidt, 2012; Schmidt et al., 2012). Talking psychotherapies for ED target explicit cognitive processes teaching patients to employ effortful and conscious strategies to divert attention from anxiety-provoking thoughts. Given the psychological components to ED, there is an indubitable need for such approaches within the field. However, given the neuroscience data and neurobiological models of ED summarised previously, there is a strong need for brain-directed treatment adjuncts to complement existing therapies in order to improve outcomes. Despite this, and the development of sophisticated neuroscience technologies, research into novel ED treatment options has remained relatively 'brainless'.

The four neuromodulatory techniques introduced previously are used in both research and clinical settings to probe, understand and alter neural activity in other disorders. The non-invasive techniques rTMS and tDCS have been most widely investigated in relation to depression (Berlim, Van den Eynde, & Daskalakis, 2012, 2013; Gaynes et al., 2014; Kalu et al., 2012; Nitsche, Boggio, et al., 2009; Shiozawa et al., 2014; Slotema, Blom, Hoek, & Sommer, 2010) whilst VNS and DBS, despite being more invasive, have shown potential in the treatment of depression, OCD, epilepsy and Parkinson's disease (DeLong & Wichmann, 2012; Holtzheimer & Mayberg, 2011; Kohl et al., 2014; Martin & Martin-Sanchez, 2012; Meneses et al., 2013). These forms of neuromodulation are widely accepted as safe and useful techniques that are highly relevant to investigations in circuit-based disorders such as ED.

In an attempt to understand the potential of neuromodulation in the treatment of ED, we have systematically reviewed the effects of rTMS, tDCS, VNS and DBS

on ED symptoms and related behaviours e.g. food intake and body weight. As has been outlined, the need for this review arises from a) the limited efficacy of existing treatments for ED, in particular enduring AN, b) the growing number of neural based models of ED, c) the variety of neuromodulation techniques being used in research and in clinical settings, d) recent studies which have applied neuromodulatory procedures in ED patients, and e) a perceived need to help direct the field of brain-directed interventions in ED.

Methods

A systematic review was conducted, following the recommendations outlined in the PRISMA guidance (Moher, Liberati, Tetzlaff, & Altman, 2009). The literature search was conducted independently by two investigators and then compared. Any disagreements were resolved by further examination of the full text and via consensus. Relevant studies were identified using online databases Pubmed, PsychInfo and Web of Knowledge. Key search terms are included below in the search strategy used in Pubmed:

((brain stimulation [Title/Abstract] OR "TMS" [Title/Abstract] OR transcranial magnetic stimulation [Mesh Terms] OR "tDCS" [Title/Abstract] OR "transcranial direct current stimulation" [Title/Abstract] OR transcranial stimulation [Title/Abstract] OR vagus stimulation [Title/Abstract] AND (food[MeSH Terms] OR food [Title/Abstract] OR eating [MeSH Terms] OR body [MeSH Terms] OR anorexia [MeSH Terms] OR anorexi [Title/Abstract] OR bulimia [MeSH Terms] OR bulimi* [Title/Abstract] OR obesity [MeSH Terms] OR obes* [Title/Abstract] OR binge eat* [Title/Abstract]))*

Searches using Web of Knowledge and PsychInfo were conducted by organising key search terms into two groups. The first group related to neuromodulation techniques for example ("brain" AND "stimulation"), "TMS", "tDCS", ("transcranial" AND "stimulation"), "VNS", ("vagus" AND "stimulation"), whilst

the second group consisted of eating disorder salient words including “food”, “eating”, “body”, “anorexia”, “bulimia”, “obesity”, “binge eat”. The first group of neuromodulation terms was crossed with each eating disorder salient word.

Initially, all of the identified articles were screened and included on the basis of relevance to the topic via inspection of their title and abstract. Publications were then cross-referenced, published review articles were examined for additional relevant studies and experts in the field were contacted in order to source any additional relevant literature. The full text versions of the remaining articles were then assessed in more detail. An overview of the literature search is shown in Figure 2.1.

Inclusion/exclusion criteria

We included articles in English (and German), dated from the earliest date available up until January 2013, that explored the effects of a form of neuromodulation on eating related outcomes e.g. ED symptoms, food cravings, eating behaviours, food intake, weight, BMI. We included studies on healthy participants (HP), people with ED, people with other psychiatric or neurological disorders and studies in animals. In addition to RCT, clinical studies, case series and case reports were included.

Several studies were excluded on the basis that their focus was not on changes to eating behaviours or body weight as a result of neuromodulation (e.g. motor excitability in Parkinson’s disease). In other cases, studies were excluded that looked primarily at the use of neuromodulation techniques as a conditioned response rather than a neuromodulatory tool. A number of other studies were excluded as they focused on the effects of neuromodulation on bodily form/perception. Whilst this is relevant to ED, it was deemed that this fell out of the scope of the present review. Finally, papers reporting on non-eating related outcomes and safety issues in ED patients (e.g. cortisol concentrations and cardiac safety), and those using an uncommon method of neuromodulation (e.g. pallidotomy) are not included.

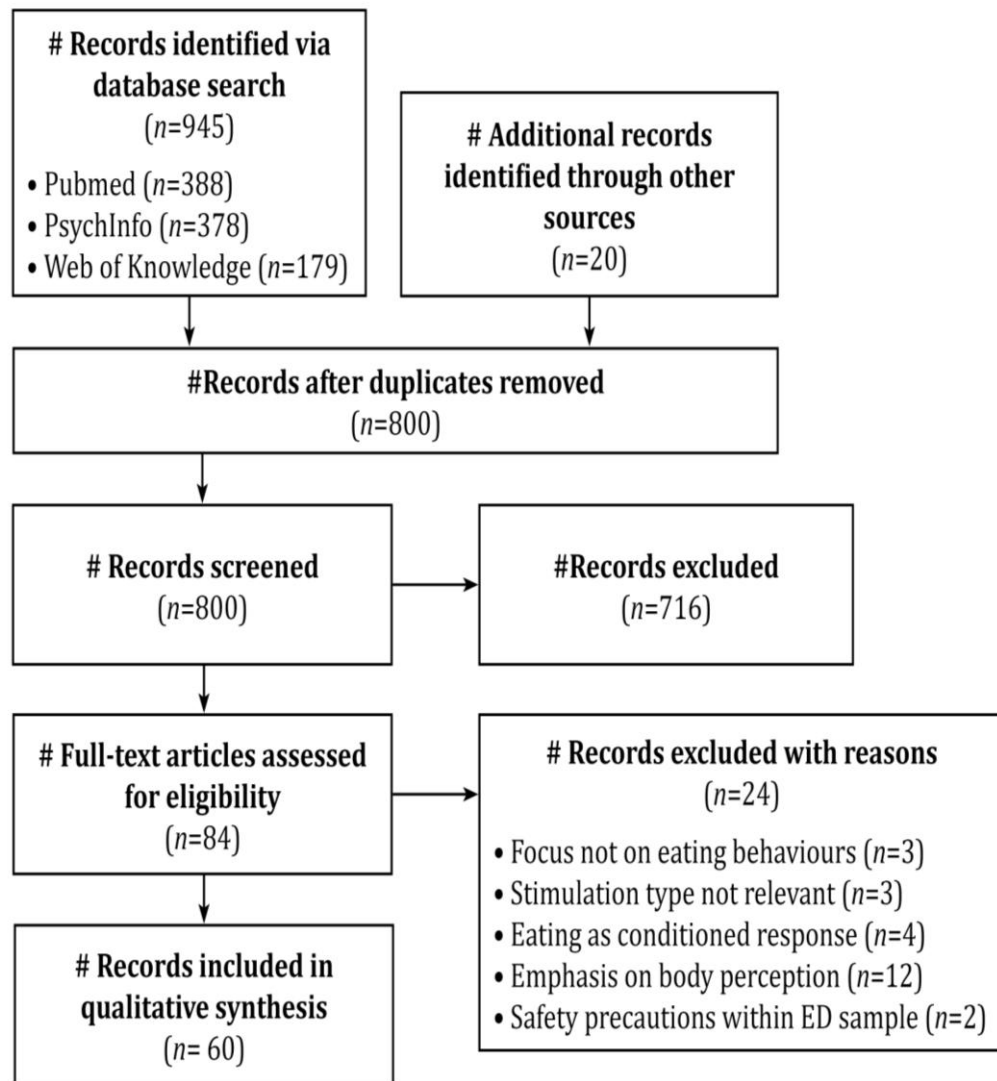


Figure 2.1 PRISMA flow chart of literature search and reviewed studies

Results

We identified 60 studies that met the inclusion criteria for this review. Five of these were conducted in HP, six were in bulimic or obese individuals, six were in AN patients, 18 were in individuals with other psychiatric or neurological disorders and 25 were animal studies. The studies that were included report effects on ED symptoms, eating behaviours, food intake and changes to body weight associated with the application of neuromodulation techniques to a number of different brain regions/structures illustrated in Figure 2.2.

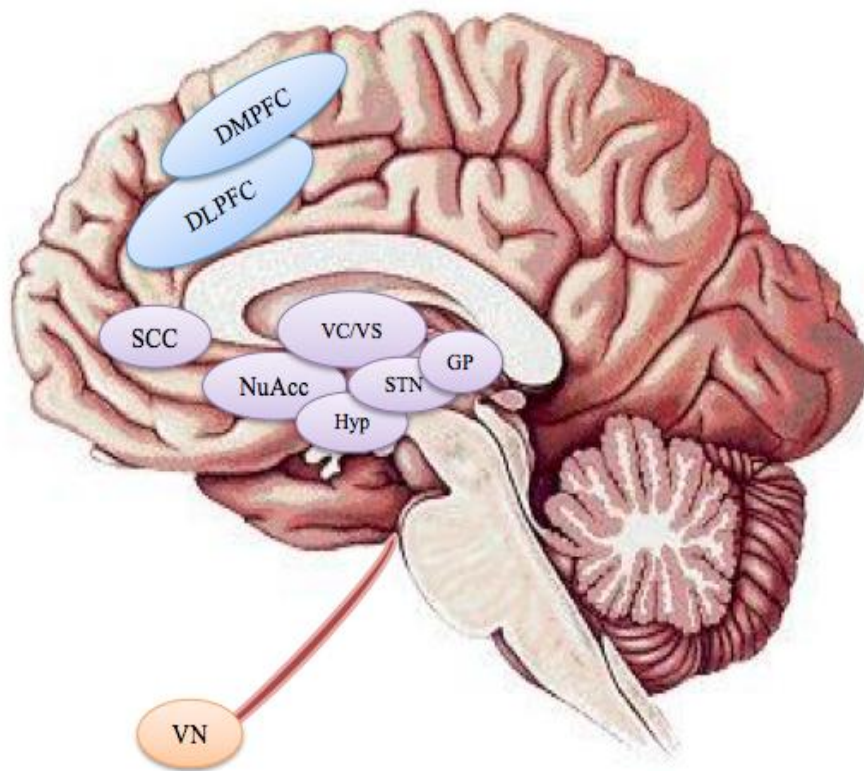


Figure 2.2 Brain areas targeted with neuromodulation in reviewed studies

Areas targeted with rTMS and tDCS (blue) are the dorsomedial prefrontal cortex (DMPFC) and the dorsolateral prefrontal cortex (DLPFC); DBS targets (purple) include the subgenual cingulate cortex (SCC), nucleus accumbens (NuAcc), ventral capsule/striatum (VC/VS), hypothalamus (Hyp), sub-thalamic nucleus (STN), globus pallidus (GP); and the vagus nerve (VN: in orange) is targeted in VNS.

Studies in healthy participants and people with frequent food cravings

Five studies in HP were identified, with four of these using individuals who reported frequent food cravings (Table 2.1). The study involving a non-food craving group, reported that compared to control conditions, active LF (1Hz) rTMS to the right DLPFC, decreased the value assigned to food (Camus et al., 2009). Given this, it is arguable that rTMS to the right DLPFC may reduce food cravings. However, following reports of a reduction in the urge to smoke (Johann et al., 2003) and cigarette consumption (Eichhammer et al., 2003) following HF (10 Hz) rTMS to the left DLPFC, two studies used a similar protocol to investigate effects on food cravings (Barth et al., 2011; Uher, Yoganathan, et

al., 2005). In an RCT of 28 individuals, food cravings during exposure to food remained stable after real rTMS and increased after sham (placebo) stimulation (Uher, Yoganathan, et al., 2005). In contrast, a cross over study with an 'improved' sham condition in ten food cravers reported that real rTMS was no better than sham in reducing cravings (Barth et al., 2011).

Building on the above studies, Fregni et al. (2008) compared both tDCS protocols; anode right/cathode left, anode left/cathode right to sham stimulation and found that food cravings reduced, remained stable or increased in these conditions respectively. Goldman et al. (2011) compared a single tDCS condition, anode right/cathode left to sham and found food cravings reduced in both conditions; however, the percentage change was greater following the active tDCS.

Studies in people with bulimia nervosa, binge eating disorder and obesity

Six studies were identified (Table 2.2) five of which investigated the effects of rTMS in patients with BN. Two single case studies of patients with BN and comorbid depression applied rTMS either to the left DLPFC (Hausmann et al., 2004) or both sides of the DMPFC (Downar, Sankar, Giacobbe, Woodside, & Colton, 2012). Both case studies reported complete recovery from binge/purge symptoms.

Three studies that involved larger samples (two are RCT) applied rTMS to the left DLPFC. A therapeutic trial of 15 sessions of HF, neuronavigated (guided by structural MRI scans) real/sham rTMS in 14 people with BN, reported improvements in binge/purge behaviours in both groups, however no difference between conditions (Walpoth et al., 2008). In a larger sample of 38 bulimic individuals, our group found that compared to sham, a single session of real HF rTMS (combined with cue exposure to food) significantly reduced right-handed patients' urge to eat and binge eating episodes over the 24 hours following stimulation: however, mood deteriorated in a series of left-handed participants (Van den Eynde, Broadbent, et al., 2012; Van den Eynde et al., 2010).

Only one study has examined neuromodulatory effects in obesity and no study was found in BED. Montenegro et al. (2012) conducted a small crossover study of anode left/cathode right tDCS versus sham stimulation, isolated or combined with aerobic exercise in nine obese individuals. Although this used an opposing stimulation protocol to studies that have reported a reduction in food cravings (anode right/cathode left tDCS), participants' desire to eat decreased after active tDCS in comparison to sham, with a greater decrease being seen when tDCS was combined with aerobic exercise.

Studies in people with anorexia nervosa

Six studies investigating the effects of neuromodulation in patients with AN were identified (Table 2.3). In a case of AN with comorbid depression, ten sessions of HF rTMS to the left DLPFC were initially administered as a treatment for depression (Kamolz, Richter, Schmidtke, & Fallgatter, 2008). As improvements in both depression and AN symptoms (including weight gain) were observed, a further 31 sessions were administered (inclusive of maintenance sessions): this resulted in a continuous improvement in both the depressive and AN symptoms. Since then, a pilot study by our group, examined the effect of a single session of real rTMS applied to the left DLPFC in 10 cases with AN and reported a reduction in levels of feeling full, feeling fat and anxiety (Van den Eynde, Guillaume, Broadbent, Campbell, & Schmidt, 2013).

Four studies were identified that used DBS to treat AN. Two cases of AN were treated with DBS for different comorbidities. In the first, there was complete remission of AN in a patient treated with DBS targeting the subgenual cingulate cortex (SCC) for co-morbid depression (Israel, Steiger, Kolivakis, McGregor, & Sadikot, 2010). Similar reductions in AN symptoms, and the maintenance of a healthy BMI was observed in another patient who underwent DBS (targeting the ventral capsule/striatum) for co-morbid OCD (McLaughlin et al., 2013).

Since these promising case reports, two groups have conducted small case series' of DBS in AN. In four acutely ill adolescent AN patients, DBS to the nucleus accumbens resulted in an average weight increase of 65% and in all

patients no longer meeting diagnostic criteria for the illness (Wu et al., 2013). A recent study applied DBS to the SCC in six treatment resistant AN patients (Lipsman et al., 2013). Nine months after DBS surgery, three patients (50%) increased and maintained their BMI greater than their historical baseline, whilst four saw improvements in AN related obsessions, mood, anxiety and affective regulation. Along with these clinical improvements, reversals in the abnormalities seen in the anterior cingulate cortex, insula and parietal lobe were accompanied by changes in cerebral glucose metabolism.

Studies assessing eating behaviours and weight in people with other psychiatric or neurological disorders

Eighteen studies applied neuromodulation to patients with other psychiatric or neurological disorders and found concurrent changes to food cravings, eating behaviours, weight and/or BMI. Findings in patients with OCD, depression and epilepsy are presented in Table 2.4, followed by studies in Parkinson's disease.

In a single case report of DBS for OCD (targeting the nucleus accumbens) the patient's weight increased by 8kg in the first few months of treatment (Mantione, van de Brink, Schuurman, & Denys, 2010). Following the initial weight increase this patient weighed 115kg and made a conscious decision to lose weight and successfully lost 44kg.

Three papers (relating to two studies) report effects of VNS on food cravings and weight changes in depressed patients. Compared to controls, significant changes to cravings of sweet foods (in both directions) between VNS on/off conditions in depressed participants were reported (Bodenlos, Kose, Borckardt, Nahas, Shaw, O'Neil, & George, 2007; Bodenlos, Kose, Borckardt, Nahas, Shaw, O'Neil, Pagoto, et al., 2007). In contrast, Pardo et al. (2007) examined the effects of VNS in depressed, obese patients and found significant, effortless weight loss proportional to BMI.

Three studies of VNS in patients with epilepsy retrospectively examined changes in weight/BMI following surgery. One study reported a significant

weight loss following VNS e.g. in 17/27 (63%) patients (Burneo, Faught, Knowlton, Morawetz, & Kuzniecky, 2002), whilst the remaining two studies reported no significant weight change following VNS for epilepsy in both adults (Koren & Holmes, 2006) and children (Kansagra, Ataya, Lewis, Gallentine, & Mikati, 2010; Koren & Holmes, 2006).

The remaining studies report (many retrospectively) changes to eating behaviours and body weight following DBS to either the sub-thalamic nucleus or globus pallidus for the treatment of Parkinson's disease. All eleven studies report either over-eating and/or increases in cravings, weight gain and increases in BMI following DBS (Bannier et al., 2009; Locke et al., 2011; Macia et al., 2004; Montaurier et al., 2007; Novakova et al., 2011; Novakova et al., 2007; Sauleau et al., 2009; Strowd et al., 2010; Tuite et al., 2005; Walker et al., 2009; Zahodne et al., 2011).

Studies assessing food intake and weight in animals

Table 2.5 summarises the 25 animal studies that investigated the effects of neuromodulation on food intake and/or body weight. Three examined the feasibility of DBS as a potential treatment for ED, specifically AN. Lacan et al. (2008) implanted the ventromedial hypothalamus of two monkeys and reported significant increases in food intake with active HF DBS compared to inactive DBS. Despite this, there was no change in body weight during the four month study period. The remaining two studies investigated the effects of DBS (sometimes referred to as electrical brain stimulation; EBS) of the lateral hypothalamus (Welkenhuysen, Van Kuyck, Das, Sciot, & Nuttin, 2008) and nucleus accumbens (van der Plasse, Schrama, van Seters, Vanderschuren, & Westenberg, 2012) in rats. The first found no significant changes to food intake but the latter reported that DBS of the medial shell of the nucleus accumbens (but not to the core or lateral shell) increased food intake by up to 250% (van der Plasse et al., 2012).

Eight studies examine the effects of VNS and DBS in binge eating/obesity animal models. Three RCT demonstrate decreased food consumption and/or lowered

weight gain in pigs following active VNS (Sobocki, Fourtanier, Estany, & Otal, 2006; Val-Laillet, Biraben, Randuineau, & Malbert, 2010) and rats (Bugajski et al., 2007).

Four studies applied DBS to the hypothalamus in rats (Sani, Jobe, Smith, Kordower, & Bakay, 2007; Torres, Chabardes, & Benabid, 2012) monkeys (Torres, Chabardes, Piallat, Devergnas, & Benabid, 2012) and pigs (Melega, Lacan, Gorgulho, Behnke, & De Salles, 2012). High-frequency DBS to the lateral hypothalamus in rats resulted in sustained weight loss (Sani et al., 2007) whilst DBS to the ventromedial hypothalamus produced mixed findings. Torres, Chabardes, and Benabid (2012) found that compared to inactive DBS, HF (130Hz) DBS increased food intake, whilst LF (30Hz) DBS reduced food intake in 27 rats. In contrast, Torres, Chabardes, Piallat, et al. (2012) found 8 hours of HF (80Hz) DBS decreased food intake in all five monkeys after fasting, and reduced body weight/BMI in three (of four) monkeys after 8 weeks of stimulation. Melega et al. (2012) administered LF DBS to the ventromedial hypothalamus in eight mini pigs given double their amount of daily food for a two month period. All animals consumed the food given, however those who received active DBS showed lower cumulative weight gain than the non-stimulated group.

As far as we are aware, only one animal study has investigated the effects of DBS on binge eating behaviours. Halpern et al. (2013) demonstrated that short term (1hr) DBS to the nucleus accumbens (but not the dorsal striatum) reduced binge eating in mice and chronic stimulation to the nucleus accumbens over four days led to a reduction in caloric intake and induced weight loss.

Four studies report changes in food intake and/or body weight in rats following VNS. These studies applied VNS for a period of 15 – 42 days. All four found a reduction in food intake, body weight/fat and/or weight gain following VNS (Banni et al., 2012; Gil, Bugajski, & Thor, 2011; Laskiewicz et al., 2003; Ziomber et al., 2009).

Finally, ten studies suggest changes in food intake and weight as a result of DBS to two areas of the hypothalamus. In general, stimulation of the lateral hypothalamus induced food intake in both cats and rats (Delgado & Anand, 1953; Halperin, Gatchalian, Adachi, Carter, & Leibowitz, 1983; Mogenson, 1971; Schallert, 1977; Stephan, Valenstein, & Zucker, 1971). However a number employed complex protocols involving comparisons with copulatory behaviours (Stephan et al., 1971) or DBS/EBS in conjunction with food deprivation (Schallert, 1977) or adrenergic interventions (Halperin et al., 1983) so their findings lack comparability. DBS/EBS to the ventromedial hypothalamus consistently reduced food intake and/or reduced weight gain (Bielajew, Stenger, & Schindler, 1994; Brown, Fessler, Rachlin, & Mullan, 1984; Lehmkuhle, Mayes, & Kipke, 2010; Ruffin & Nicolaidis, 1999).

Discussion

This review provides evidence that neuromodulation has potential for altering disordered eating behaviours, food intake and body weight. Non-invasive neuromodulation techniques (rTMS, tDCS) have been shown to prevent and reduce cravings in individuals who report frequent food cravings and rTMS applied to the PFC also has shown promise for reducing BN symptoms. In AN, the data also demonstrate potential for symptom improvement including weight gain, following both rTMS and DBS. Furthermore, reports of significant weight gain following DBS for Parkinson's disease and in animal models provide grounds for investigating the use of DBS in AN, whilst evidence suggests that VNS may have potential as an alternative bariatric intervention.

Methodological considerations

Findings reported in this review must be interpreted in the context of the varying methodologies considered. Four different techniques, rTMS, tDCS, VNS and DBS have been reviewed and within each exists the potential for a wide range of protocols. Each technique has the ability to suppress/enhance neural activity via a number of different parameters - frequency, duration, intensity,

number of pulses, number of sessions and stimulation sites. Such differences may help explain why some studies report no changes in ED symptoms or weight following neuromodulation (Barth et al., 2011; Kansagra et al., 2010; Koren & Holmes, 2006; Walpoth et al., 2008). The degree to which studies vary from one another methodologically, also limits their comparability and hence the generalisability of these findings. On the other hand, the number of neuromodulatory techniques available and the wide range of protocol options possible within each, means that the field is advancing along a broad front.

Further studies on the neural effects of neuromodulation are needed to optimise protocols: these are likely to arise from research involving online neuroimaging/neuromodulation. Data from animal models are also important, but must be interpreted with caution as factors such as the ratio of neuromodulation device (e.g. TMS coil size) to head size, coil orientation, anaesthesia and mechanical restraint are just a few elements that need to be considered when findings are extrapolated to humans (Vahabzadeh-Hagh, Muller, Gersner, Zangen, & Rotenberg, 2012). Finally, although limited by issues of stimulation focality and differences between animal and human brains, animal models are likely to provide important information on the mechanisms of neuromodulation and their potential for use in the treatment of ED.

Repetitive Transcranial Magnetic Stimulation

rTMS has been investigated in healthy individuals, those reporting frequent food cravings, and in patients with BN and AN. Most of this work has involved HF (excitatory) rTMS to the left PFC. The studies demonstrate its promise in stabilising food cravings during food exposure, and reducing both BN and AN symptoms. Arguably, this may result from restoring altered 'top-down' cognitive control in relation to emotional and other self-regulation processes. Given the demonstrated ability of rTMS to modulate food cravings and binge eating episodes, in addition to its non-invasive, safe and relatively tolerable nature it is perhaps surprising that no studies have investigated its potential in BED or obesity. Lastly, given the chronic and life-threatening nature of AN and the

promising data on rTMS in AN, larger, sham controlled studies are needed (see Chapter 3).

The use of neuroimaging techniques in ED is likely to increase knowledge of the neural correlates of disordered eating and this will enable refinement and optimisation of rTMS protocols for treating specific ED. In particular, the role of right fronto-temporal circuits in ED as outlined in a review of brain lesions in ED (Uher & Treasure, 2005) and reports of ED resolution following right temporal lobe injuries (Levine, Lipson, & Devinsky, 2003) suggest that right sided rTMS may be equally, if not more effective than the predominately left sided rTMS protocols.

Transcranial Direct Current Stimulation

Increased knowledge on the role of hemispheric lateralisation in ED, together with improvements in the design of neuromodulation protocols is likely to emerge from studies involving tDCS. To date, most tDCS research has been in relation to food cravings and has shown that excitation of the right/inhibition of the left PFC reduces cravings during cue exposure. Stabilisation of cravings during exposure was observed with the opposite tDCS protocol, which is somewhat consistent with the rTMS literature. The idea that increasing activity in the right PFC may decrease cravings/appetite and re-establish control over eating is also consistent with the right brain hypothesis of obesity (Alonso-Alonso & Pascual-Leone, 2007). It is possible that there is some type of inter-hemispheric imbalance in conditions involving cravings and over eating, but more neuroimaging based evidence is required.

In comparison, the idea of right hemispheric dominance in AN, specifically hyperactivity in the right frontal regions, is somewhat established, and it is possible that anodal left/cathodal right tDCS may aid in altering/resetting inter-hemispheric balance (Hecht, 2010). This is consistent with the TMS literature in AN, which shows symptom reduction following excitation of the left DLPFC. By comparing the two possible tDCS designs to sham tDCS in AN, the possible role

of hemispheric lateralisation in the illness may be elucidated. As in the case of rTMS, there is a need for more investigations of tDCS within ED populations.

Vagus Nerve Stimulation

Evidence from the use of VNS in other psychiatric and neurological disorders and in animal studies supports the argument for more investigations in ED, especially obesity. Whilst VNS seems to have induced weight loss in a proportion of participants with depression, obesity or epilepsy, VNS in animals has consistently been associated with reductions in food intake and/or weight loss.

The vagus nerve is the major neural pathway carrying information to the gastrointestinal tract. In the current review, VNS has been associated with changes in food intake and resulting body weight suggesting that vagal stimulation mediates satiety signals. Given the increasing prevalence, high morbidity and mortality of obesity, VNS has potential as an alternative to more invasive treatments for morbid obesity, which are often associated with severe side-effects and unsustainable weight loss.

Deep Brain Stimulation

DBS has been used in a number of treatment studies of AN, in part as a result of emerging neural based models of AN. The results are promising – two case reports resulting in remission of the illness, and two case series resulting in increases in body weight and reductions in symptoms in most patients. Furthermore, the reviewed cases have demonstrated DBS to be a safe procedure with minor side effects. Existing studies of DBS in AN have targeted a variety of different brain structures and thus more research is needed in order to establish optimal DBS targets. Moreover, larger controlled trials are needed to establish the long term efficacy of DBS in this difficult to treat population.

Weight gain following DBS for Parkinson's disease has implications for the use of DBS in AN. Although the reduction in motor activity (e.g. tremors) as a result

of DBS may contribute to resulting weight gain, two studies found no correlation between weight gain and reduced motor activity following DBS (Locke et al., 2011; Montaurier et al., 2007). A number of explanations have been proposed including the suggestion that the DBS current may spread to the hypothalamic satiety centres. In support of this, a number of animal studies report increases in food intake and/or body weight following DBS to the lateral hypothalamus. In contrast, stimulation to the ventromedial hypothalamus shows the opposite, particularly when applied at lower frequencies. Interestingly, two studies showed lower rates of weight gain in stimulated animals despite no changes in the amount of food consumed, suggesting that DBS may alter metabolic rate (Lehmkuhle et al., 2010; Melega et al., 2012).

Considerations for neuromodulation in eating disorders

ED are complex, multifaceted mental illnesses, associated with altered thinking and beliefs, heightened fear and anxiety responses, mood disturbances and a myriad of other symptoms. The ED are therefore not simply about eating. Although this review reports solely on the effects of neuromodulation on eating related behaviours and resulting weight gain/loss, such changes are likely to arise as a result of effects to some of the underlying cognitive, emotional and self-regulatory aspects of ED, such as cognitive rigidity, impaired decision making, poor inhibition and altered self-control. Such traits are proposed to be caused by the same dysfunctional fronto-subcortical circuits (Celone et al., 2011; Marsh et al., 2011; Marsh, Maia, et al., 2009; Marsh, Steinglass, et al., 2009; Sato et al., 2013). Neuromodulation is likely to alter such neurocognitive impairments in ED, however further investigations employing neuropsychological outcomes are required (see Chapter 4).

Changes in neuropsychological aspects of ED following neuromodulation may also result from alterations associated with neuroplasticity. Studies in animals have demonstrated that repeated sessions of HF rTMS induce long-lasting effects in neuroplasticity (Gersner, Kravetz, Feil, Pell, & Zangen, 2011). Such findings have implications for intractable, neuro-circuit disorders such as AN.

Changes in neuroplasticity highlight the potential of including exposure therapies with neuromodulation protocols in ED, to facilitate extinction learning (Koskina, Campbell, & Schmidt, 2013). In rats, HF rTMS paired with exposure to a conditioned stimulus facilitated fear extinction up to 24 hours post stimulation (Baek, Chae, & Jeong, 2012). Whilst a number of studies reviewed here include exposure to highly palatable foods immediately before and after neuromodulation, online approaches applying neuromodulation during exposure tasks may bolster outcomes.

Similarly, individual differences in cortical plasticity have been shown to modulate the behavioural effect of neuromodulation (Plewnia et al., 2013). Research into individual neural patterns will enable more precise, personalised protocols for rTMS, tDCS, VNS and DBS. Altering neuromodulation parameters such as stimulation site and frequency (excitatory/inhibitory) as a result of a better understanding of hemispheric lateralisation and hyper- or hypo-activity of certain brain regions is one likely possibility. In addition, brain imaging could be used to identify biomarkers of treatment response and thus individualised neuromodulation foci.

Such neural targets may include the insula and other sub-cortical structures involved in emotional responses and reward processing, and implicated in brain imaging ED research. However, the neural effects of common non-invasive neuromodulation techniques such as rTMS and tDCS are thought to be limited to the outer cerebral cortex. Continuing innovation within the neuromodulation domain has led to the development of tools with both improved focality and a greater depth of modulatory effects. Deep TMS operates on the same principle of electromagnetic induction as standard TMS. However, the standard TMS figure-of-eight coil alters cortical excitability up to a depth of 1.5-2.5cm. In comparison, the most widely used and safety tested deep TMS coil – the H-coil – exerts neuromodulatory effects up to 6cm from the scalp (Bersani et al., 2013). Early evidence suggests that patients with treatment resistant depression who are also ECT non-responders may benefit from deep TMS (Rosenberg, Zangen, Stryjer, Kotler, & Dannon, 2010). Deep TMS may therefore have a place in future

ED neuromodulation applications. Modulation of both the cerebral cortex and limbic neural circuits that deep TMS may induce could enable changes to both the dysfunctional 'top-down' dorsal circuits as well as the 'bottom-up' ventral systems proposed to underlie ED. Similarly, building on advances from TMS research, magnetic seizure therapy (MST) induces a seizure via HF rTMS. Despite the same final outcome as ECT i.e. a 'therapeutic' seizure – increased stimulation focality, lessened side effects in conjunction with similar antidepressant response rates to ECT, have been found in the early stage of MST investigations, indicating that this a preferable alternative (Hoy et al., 2013).

Overall summary

Increasing knowledge of the neural underpinnings of ED, and the evidence emerging from neuromodulation studies indicates that treatments for ED should not remain 'brainless'. Although neuromodulation treatments are unlikely to be stand-alone treatments for ED or obesity, this review demonstrates the potential of rTMS, tDCS, VNS or DBS to improve outcomes. In particular, reducing problematic eating behaviours and promoting weight gain in enduring and chronic cases of AN seems feasible via the use of neuromodulation techniques.

Table 2.1 Neuromodulation studies in healthy participants and people with frequent food cravings

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Camus et al (2009)	56	HP Right-handed	rTMS	RCT parallel, blinded i) real to right DLPFC, 2 controls: ii) real to vertex & iii) sham to right DLPFC	Right-DLPFC & vertex	1Hz, 15min 50% output 900 pulses 1 session Neuronavigated	Compared to control conditions, real rTMS to right DLPFC decreased the value assigned to food stimuli	
Uher et al (2005)	28	HP Right-handed Frequent food cravings	rTMS	RCT parallel, double blind i) real vs. ii) sham	Left-DLPFC	10Hz, 20min, 110% MT 1000 pulses 1 session 5cm anterior method	Food cravings with food exposure remained stable after real rTMS & increased after sham rTMS.	
Barth et al (2011)	10	HP Frequent food cravings	rTMS	RCT crossover, blinded, i) real vs. ii) sham	Left-DLPFC	10Hz, 15min, 100% MT 3000 pulses 1 session of each condition 5cm anterior method	Real rTMS reduced cravings no better than sham.	Improved sham condition: matched to individuals perceived pain.

HP: healthy participants; rTMS: repetitive transcranial magnetic stimulation; RCT: randomised control trial; DLPFC; dorsolateral prefrontal cortex; Hz: Hertz; min: minutes; MT: motor threshold

Table 2.1 (continued) Neuromodulation studies in healthy participants and people with frequent food cravings

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Fregni et al (2008)	23	HP Frequent food cravings	tDCS	RCT crossover double blind 2 active conditions: i) anode left/cathode right, ii) anode right/cathode left vs. iii) sham	DLPFC	2mA, 20min 1 session of each condition 10-20 EEG system (F3 for left DLPFC, F4 for right DLPFC)	Cravings decreased with anode right/cathode left, remained stable with anode left/cathode right & increased after sham. Subjects fixated (eye-tracking) on food-related pictures less after anode right/cathode left. Subjects consumed less food after both types of active stimulation.	
Goldman et al (2011)	19	HP Frequent food cravings	tDCS	RCT crossover, blinded i) anode right/cathode left, vs. ii) sham	DLPFC	2mA, 20min 1 session of each condition 10-20 EEG system (F3 for left DLPFC, F4 for right DLPFC)	Food cravings reduced in both conditions; percentage change significantly greater in active tDCS. Active tDCS reduced cravings for sweet foods & carbohydrates more than sham. No difference between groups in amount of food ingested.	

HP: healthy participants; tDCS: transcranial direct current stimulation; RCT: randomised control trial; DLPFC: dorsolateral prefrontal cortex; mA: milliamps; min: minutes; EEG: electroencephalography

Table 2.2 Neuromodulation studies in people with bulimia nervosa and in obese individuals

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Hausmann et al (2004)	1	BN/DP	rTMS	Case report	Left-DLPFC	20Hz, ~12min, 80% MT 10 sessions; 2 per weekday for 2 weeks Neuronavigated	Complete recovery from binge/purge symptoms & ~50% decrease in depression scores.	
Walpoth et al (2009)	14	BN	rTMS	RCT parallel double blind i) real vs. ii) sham	Left-DLPFC	20Hz, ~12min, 120%MT Total of 30000 pulses 2000 pulses per/session 15 sessions; 1 per weekday for 3 weeks Neuronavigated	Improvement in self-reported binge/purge behaviours, depressive & OCD symptoms in both groups. No difference between real & sham groups.	
Van den Eynde et al (2010)	38	BN Right-handed	rTMS	RCT parallel double blind i) real vs. ii) sham	Left-DLPFC	10Hz, 20min, 110% MT 1000 pulses 1 session 5cm anterior method	Compared to sham, real rTMS was associated with a decrease in self-reported urge to eat & binge eating (24hrs post session).	
Van den Eynde et al (2012)	7	BN Left-handed	rTMS	Case series All received real despite being told they might receive real or sham. Compared to group in above study.	Left-DLPFC	10Hz, 20min, 110%MT 1000 pulses 1 session 5cm anterior method	Left-handed group: decrease in reported cravings whilst urge to eat remained stable. Mood deteriorated in the left-handed group yet improved in the right handed group. No difference between right & left handed groups in urge to eat, urge to binge, tension or hunger.	

BN: bulimia nervosa; DP: depression; rTMS: repetitive transcranial magnetic stimulation; RCT: randomised control trial; DLPFC: dorsolateral prefrontal cortex; HZ: Hertz; min: minutes; MT: motor threshold; OCD: obsessive compulsive disorder; hrs: hours

Table 2.2 (continued) Neuromodulation studies in people with bulimia nervosa and in obese individuals

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Downar et al (2012)	1	BN/DP	rTMS	Case report	DMPFC (both)	10Hz, 15min, 120% MT 3000 pulses 40 sessions in total Neuronavigated a) 20sessions; 1 per weekday for 4 weeks b) Repeat second course requested (20)	a) Full remission of binge/purge episodes & depression for more than 2 months post treatment completion. b) After significant life stressor, requested repeat course. Remained in remission from ED and depression.	Full remission for 64 days. Three single binge/purge episodes due to significant psychosocial stressor leading to repeat course.
Montenegro et al (2012)	9	OB	tDCS	RCT crossover, blinded i) sham/anodal left DLPFC, ii) sham/anodal left DLPFC+ exercise	DLPFC	2mA, 20min, 1 session of each condition 10-20 EEG system (F3 for left DLPFC)	Compared to sham, active anodal left DLPFC tDCS decreased desire to eat. Anodal left tDCS + aerobic exercise led to greater suppression of desire to eat than tDCS/exercise alone.	

BN: bulimia nervosa; DP: depression; OB: obese; rTMS: repetitive transcranial magnetic stimulation; tDCS: transcranial direct current stimulation; RCT: randomised control trial; DMPFC: dorsomedial prefrontal cortex; DLPFC: dorsolateral prefrontal cortex; Hz: Hertz; min: minutes; MT: motor threshold; mA: milliamps; EEG: electroencephalography; ED: eating disorder

Table 2.3 Neuromodulation studies in people with anorexia nervosa

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Kamolz et al (2008)	1	AN/DP	rTMS	Case report	Left-DLPFC	10Hz, 20min, 110% MT 2000 pulses 41 sessions in total 10-20 EEG system (F3) a) 10 sessions/16 days b) deterioration 10 days post treatment; 6 more sessions c) requested third course of 10 sessions d) maintenance; 15 sessions, 2 p/week for 8 weeks	a) Improvement in depressive & ED symptoms e.g. uncomplicated food intake and weight gain. b) Reduction in depressive symptoms c) Significant reduction in depressive symptoms and eating programme effective after these ten sessions. d) Continuous improvement of depression and ED symptoms.	Maintenance sessions required to reduce the chance of a second relapse.
Van den Eynde et al (2011)	10	AN Right handed	rTMS	Case series All received real despite being told they might receive real/sham.	Left-DLPFC	10Hz, 20min, 110% MT 1000 pulses 1 session 5cm anterior method	Real rTMS resulted in reduced levels of feeling full, fat, and anxiety. Trend towards a decrease in urge to exercise. No difference in urge to restrict, urge to eat, mood, tension and hunger.	
Israel et al (2010)	1	AN/DP	DBS	Case report	SCC Bilateral	Right-sided intermittent, 2min on/1min off 130Hz, 5mA, 91µS	Remission of ED, no relapse and maintained average BMI of 19.1. Remission from ED remained despite depressive breakthroughs.	Pharmacological treatments continued post-operatively.

AN: anorexia nervosa; DP: depression; rTMS: repetitive transcranial magnetic stimulation; DBS: deep brain stimulation; DLPFC: dorsolateral prefrontal cortex; SCC: subgenual cingulate cortex; Hz: Hertz; min: minutes; MT: motor threshold; EEG: electroencephalography; mA: milliamperes; µS: microseconds; ED: eating disorder; BMI: body mass index

Table 2.3 (continued) Neuromodulation studies in people with anorexia nervosa

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Wu et al (2012)	4	AN	DBS	Case series	NuAcc bilateral	-	Average of 65% increase in body weight at 38 month follow-up. All patients weighed >85% of expected body weight, menstruation restored & no longer meet the AN diagnostic criteria. Depression & OCD symptoms improved.	Patients age 16-17 years, duration of illness 13-28 months. All had psychiatric co-morbidities.
McLaughlin et al (2012)	1	AN/OCD	DBS	Case report	VC/VS Bilateral	120Hz, 7.5V, 120 μ S Monopolar	There was reduction in food/eating related concerns. Food intake, food variety & body weight were increased. BMI maintained between 18.9 – 19.6	Symptoms worsened when cathode electrode added.
Lipsman et al (2013)	6	AN	DBS	Prospective case series	SCC	130Hz, 5-7V, 90 μ S	At 9 month follow-up, 3 patients (50%) increased & maintained BMI greater than their historical baseline. Improvement in food/weight preoccupations, mood, anxiety, affect regulation & quality of life. Changes in cerebral glucose metabolism & reversal of abnormalities in variety brain regions.	Patients age 20-60 years, treatment resistant. Side effects include: panic attacks, nausea, air embolus, pain and seizure (1 patient only).

AN: anorexia nervosa; OCD: obsessive compulsive disorder; DBS: deep brain stimulation; NuAcc: nucleus accumbens; VC/VS: ventral capsule/striatum; SCC: subgenual cingulate cortex; Hz: Hertz; V: volts; μ S: microseconds; BMI: body mass index

Table 2.4 Neuromodulation studies assessing eating behaviours and/or body weight in other psychiatric and neurological disorders

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Mantione et al (2010)	1	OCD	DBS	Case report	NuAcc	185 Hz, 3.5V, 90µs Monopolar	First few months' post-surgery weight gain of 8kg. Then after conscious decision to lose weight (weighing 115kg), 10 months after dieting was at target weight of 71kg (BMI = 25). Maintained weight at 2 years follow-up.	Simultaneous effortless smoking cessation.
Bondelos et al (2007a, b)	33	DP	VNS	a) Between groups comparison: i) depression VNS, ii) depression non-VNS, iii) HC b) Within VNS group: crossover, blinded VNS i) on versus ii) off	Left VN	20Hz, 1.25mA 0.5-84 months 1 session	Groups did not differ in mean food cravings & their ability to resist food. Between viewing food images, cravings for sweet foods differed between groups: depressed-VNS had higher change scores for craving of sweets than depression non-VNS and HC.	In VNS group cravings for sweets changed in both directions. Decrease in six participants, increase in five.
Pardo et al (2007)	14	DP/OB	VNS		Left VN	30Hz, 0.25-1.5mA, 250 or 500µs 30sec on/ 5 min off 24 months	Significant, effortless weight loss proportional to initial BMI. Stimulation parameters had no effect on weight changes.	
Burneo et al (2002)	27	EP	VNS	Retrospective	Left VN	-	Significant weight loss (>5%) in 17 patients. Remaining patients had no significant change in weight.	

OCD: obsessive compulsive disorder; DP: depression; OB: obesity; EP: epilepsy; DBS: deep brain stimulation; VNS: vagus nerve stimulation; HC: healthy controls; NuAcc: nucleus accumbens; VN: vagus nerve; Hz: Hertz; V: volts; µS: microseconds; mA: milliamps; sec: seconds; min: minutes; BMI: body mass index; HC: healthy controls

Table 2.4 (continued) Neuromodulation studies assessing eating behaviours and/or body weight in other psychiatric or neurological disorders

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Koren et al (2006)	21	EP	VNS	Retrospective	Left VN	30Hz, 1.25-3mA, 500µs 30sec on & 5sec off 24 months	No significant change in weight within 2 years following VNS implantation.	
Kansagra et al (2010)	23	EP(c)	VNS	Retrospective	Left VN	-	No significant changes in BMI at 1 year and final time point (mean 4.2 years) following VNS implantation.	
Macia et al (2004)	33	PD	DBS	Retrospective PD DBS (n=19) vs. PD non-DBS (n=14)	STN	130Hz, 1.5-3V, 90µs Monopolar	18/19 DBS patients had significant weight gain and increase in BMI. Significant reduction in resting EE, no change in daily EE	
Tuite et al (2005)	27	PD	DBS	Retrospective	STN	-	Significant weight gain up to 12 months after surgery.	
Novakova et al (2007)	25	PD	DBS	Retrospective	STN Bilateral	-	Average weight gain of 9.4kg during first follow-up at 1-45 months post- implantation. One year later, decrease in 12 patients, increase in 6 & 3 remained stable.	
Montaurier et al (2007)	23 24	PD HS	DBS	Prospective	STN Bilateral	148.0Hz, 2.7-2.8V, 69µs	Increase in body weight & fat mass after surgery. Daily EE decreased significantly.	No correlation between reduced EE and weight gain

EP: epilepsy; EP(c): children with epilepsy; PD: Parkinson's disease; VNS: vagus nerve stimulation; DBS: deep brain stimulation; VN: vagus nerve; STN: sub-thalamic nucleus; Hz: Hertz; mA: milliamps; µs: microseconds; sec: seconds; V: volts; BMI: body mass index; EE: energy expenditure; kg: kilograms

Table 2.4 (continued) Neuromodulation studies assessing eating behaviours and/or body weight in other psychiatric or neurological disorders

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Walker et al (2009)	39	PD	DBS	Retrospective	STN Unilateral	-	Compared to preoperative baseline, weight increased by mean of 4.3kg 1 year following surgery.	
Bannier et al (2009)	22	PD	DBS		STN		68% patients overweight/obese 3 months post-surgery, increased to 82% at 16 months post-surgery.	
Sauleau et al (2009)	46	PD	DBS	DBS to STN (n=32) versus DBS to GPi (n=14)	STN/GP	130Hz, 60µs	Significantly higher increase in BMI in STN DBS patients.	
Strowd et al (2010)	182	PD	DBS	Retrospective	STN/VIM/GP	-	Significant weight gain up to 24 months post-surgery, not predicted by stimulation target.	
Novakova et al (2011)	27	PD	DBS		STN	-	Significant weight gain during 12 month post-implantation.	
Locke et al (2011)	52	PD	DBS	Retrospective	STN/GP Unilateral	-	Significant weight gain following surgery, no significant difference in weight gain between GP & STN targets.	No correlation between reduced motor scores & weight gain.
Zahodne et al (2011)	100	PD	DBS	Prospective	STN/GP	-	DBS implantation predicted over eating & an increase in cravings.	

PD: Parkinson's disease; DBS: deep brain stimulation; STN: sub-thalamic nucleus; GP, globus pallidous; VIM: ventralis intermedius nucleus; Hz: Hertz; µs: microseconds; kg: kilograms

Table 2.5 Neuromodulation studies assessing food intake and/or weight in animals

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
<i>Animal models of anorexia nervosa</i>								
Lacan et al (2008)	2	Monkeys	DBS	2 cycles of stimulation a) 8 days of active, 2 days of inactive, b) 3 days active, 3 days inactive.	vmH Bilateral	a) 185Hz, 2.5V, 90µsec b) 185 Hz, 3.5V, 90 µsec	Significant increase in food intake during active stimulation. There was no change in body weight.	
Welkenhuysen et al (2008)	26	Rats	EBS (DBS)	a) Acute: 4 subsequent sessions conducted in random order of amp. b) Chronic: on/off	Lateral Hypoth.	a) 100 Hz, 0.06 msec, 3.5hrs 0, 25%, 50% and 75% amp. b) 100Hz, 0.06msec pulses, 50% maximum amplitude	a) Decrease in the number of wheel rotations (lower activity levels), but no impact on food intake. b) No effect on wheel rotations, or amount of food consumed.	
Van der Plasse et al (2012)	8	Rats	DBS	Comparison of DBS to 3 areas of NAcc i) core, ii) lateral shell (lShell) and iii) medial shell (mShell)	NAcc	130Hz 60µS pulses 200µS off 300µm electrodes	DBS to core had no effect on response to sucrose or food intake, to lShell reduced motivation to respond for sucrose, no effect on food intake. DBS to mShell profoundly increased food intake (250% of baseline).	Implications for medial shell of NAcc as target for DBS in AN.

DBS/EBS: deep/electrical brain stimulation; vmH: ventromedial hypothalamus; Hypoth: hypothalamus; NuAcc: nucleus accumbens; Hz: Hertz; V: volts; µS: microseconds; msec: milliseconds; BMI: body mass index; EE: energy expenditure.

Table 2.5 (continued) Neuromodulation studies assessing food intake and/or weight in animals

N	Sample	Type	Design	Area	Protocol	Findings	Comments	
<i>Animal models of binge eating and obesity</i>								
Sobocki et al (2006)	8	Pigs	VNS	RCT crossover design i) 4weeks on vs. ii) 4weeks off	Anterior VN	34Hz,4V,0.5ms, every 3-4 hours for 24hours	In both groups, cumulative body weight gain was lower during stimulation period compared to the control period.	Metabolic rate not affected.
Bugajski et al (2007)	18	Rats	VNS	RCT 3 groups i) active VNS, ii) inactive VNS, iii) no VNS	Left VN Unipolar	0.05Hz, 200mV, 10ms pulses 100 days	Significant decrease in meal size, fat weight and weight gain in VNS rats compared to controls.	
Val-Laillet et al (2010)	8	Mini Pigs	VNS	RCT i) real vs. ii) sham	VN	30Hz,2mA, 500μS 30sec on/5min off 14 weeks	VNS implantation resulted in animals' weight remaining stable, decreased food consumption & sweet food cravings compared to animals with sham implants.	
Sani et al (2007)	16	Rats	DBS	RCT i) active continuous stimulation vs. ii) implanted inactive	Lateral Hypoth.	180-200 Hz,2.0 V, 100msec pulse width, ~31 days	Significant decrease in weight gain in the stimulated compared to the non-stimulated group.	

VNS: vagus nerve stimulation; RCT: randomised control trial; VN, vagus nerve; Hypoth: hypothalamus; Hz: Hertz; V: volts; msec; milliseconds; mV: millivolts; mA: milliamps; µS: microseconds; sec: seconds; min: minutes

Table 2.5 (continued) Neuromodulation studies assessing food intake and/or weight in animals

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Torres et al (2011)	27	Rats	DBS	Unilateral continuous, bipolar stimulation a) Acute: HF (130Hz) vs. LF (30Hz) b) Chronic: long term effects of HF	vmH	30-130Hz, 60ms, 222±103µA a) 30min b) 16 days, 4hrs/day, 5 days/wk, 3 weeks	a) Acute HF increased food intake compared to sham. Acute LF reduced food intake compared to sham. b) Chronic stimulation (130Hz) slowed down body weight intake compared to sham.	
Torres et al (2012)	5	Monkeys	DBS	a) Acute: various DBS parameters post 24hr fasting, vs. inactive, b) Chronic: 8 week trial of 3 protocols	Hypoth.	a) 30-130Hz, 8hrs b) 30Hz, 80Hz, 130Hz continuous stimulation day/night for 8 weeks.	a) Decreased food intake for all MK at 80Hz b) Significant decrease in body weight and BMI at 80Hz. Skinfolds reduced at 80Hz yet increased at 130Hz. Sham MK increased their weight.	Intraventricular approach
Melega et al (2012)	8	Mini Pigs	DBS	2 groups: i) active versus ii) inactive	vmH Bilateral	50Hz, 8 weeks, 507 µs 0.5mA, 1.0mA, 1.5mA	All animals ate the same amount of food, yet those that received active DBS had less cumulative weight gain than non-stimulated animals.	DBS may be associated with increase in metabolic rate.
Halpern et al (2013)	73	Mice	DBS	Randomised design a) binge eating: surgical and non-surgical mice b) acute DBS to NAcc shell or dorsal striatum c) chronic DBS in obese mice	NuAcc shell	a) 160Hz, 150µA, 60µS pulses, 1hr b) 160Hz, 150µA, 60µS pulses for 4 days	DBS to NAcc shell reduced binge eating and increased c-Fos levels in this area (measure of neuronal activity). Dopamine receptor D2 attenuated action of DBS. DBS to dorsal striatum had no influence on binge eating. Chronic DBS to obese mice reduced caloric intake & induced weight loss.	Implicates mesolimbic dopamine pathways in hedonic aspects of obesity.

DBS: deep brain stimulation; HF: high frequency; LF: low frequency; Hz: Hertz; hr(s): hour(s); vmH, ventromedial hypothalamus; Hypoth: hypothalamus; ms: milliseconds; µA: microamps; µS: microseconds; mA: milliamps; min: minutes

Table 2.5 (continued) Neuromodulation studies assessing food intake and/or weight in animals

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
<i>Other studies in animals</i>								
Laskiewicz et al (2003)	60	Rats	VNS	5 conditions: i) left vagal (0.5Hz), ii) both vagal nerves (0.5Hz), iii) left vagal (0.1Hz), iv) both vagal nerves in obese rats (0.1Hz), v) left vagal & right side abdominal vagotomy	Left and right VN	0.05 and 0.1 Hz, 0.55 V, 0.1sec for 27days	Body weight and total food intake decreased in all conditions. Effects of both vagal nerves stimulation on final body weight & food intake significantly more effective than only one single nerve.	
Ziomber et al (2010)	78	Rats	VNS	3 conditions i) active in the magnetic field exposure (MFE), vs.2 control groups with inactive solenoid without electrodes ii) in the MFE iii) outside the MFE	Left VN	0.1, 0.2, 0.5 and 1.0Hz 50, 100, 150 and 200mV Stimulation changed every 3 days for 15 days	Rats with solenoid electrodes significantly decreased their food intake, weight gain & serum leptin concentrations when compared to controls.	
Gil et al (2011)	24	Rats	VNS	Randomised into 3 groups: i) active ii) inactive and iii) non-operated controls	Left VN	10Hz, 200mV, 10ms 12hrs/day, 42 days	Active VNS stimulation reduced daily and total food intake, body weight and body fat compared to both inactive & control group. No difference in food intake or body fat between inactive & control condition.	

DBS: deep brain stimulation; VNS; vagus nerve stimulation; NuAcc: nucleus accumbens; VN: vagus nerve; Hz: Hertz; μ A: microamps; μ S: microseconds; hr: hour; V: volts; sec: seconds

Table 2.5 (continued) Neuromodulation studies assessing food intake and/or weight in animals

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Banni et al (2012)	10	Rats	VNS	2 naïve, 4 sham, 4 VNS rats compared across a) acute (3hr) & b) chronic (4 weeks)	Left VN	30Hz, 1.50mA 30sec on/5 min off	Compared to sham, chronic VNS reduced food intake, body weight gain & amount of adipose tissue.	
Delgado et al (1953)	6	Cats	DBS	a) Control period 1-2 weeks before implantation vs. b) bipolar stimulation	Lateral Hypoth	60Hz, 0.2 μ s, 1-5 V 0.5sec, every 5sec, 1hr 5-10 days	Daily stimulation produced increase in food intake.	
Stephan et al (1971)	14	Rats	EBS (DBS)	On versus off stimulation	Lateral Hypoth	10-60 μ A, 0.5min on/1min off 20 trials	50% of rats displayed stimulation bound eating.	Emphasis on copulation behaviours.
Mogenson et al (1971)	75	Rats	EBS (DBS)	-	Lateral Hypoth	60Hz, 6-30 μ A, 5sec on/15 sec off, 30min	Stimulation of the lateral hypothalamic area induced feeding and/or drinking in 30 rats.	
Schallert et al (1977)	38	Rats	EBS (DBS)	Food and water deprivation versus brain stimulation	Lateral Hypoth	100Hz, 30-90 μ A, 0.2msec, 1min on/30sec off	Rats not attracted to food stimuli when undeprived, nor with stimulation alone. When deprived from food/water & stimulated became attracted to food stimuli.	
Halperin et al (1983)	8	Rats	EBS (DBS)	4 conditions: i) saline, inactive EBS, ii) adrenergic, inactive EBS, iii) saline, active EBS, iv) adrenergic, active EBS	Left lateral Hypoth	60Hz, 14-104 μ A 30sec on/30sec off, 20 trials	With combined adrenergic and EBS food intake was significantly greater than to either condition alone.	

VNS: vagus nerve stimulation; DBS/EBS: deep/electrical brain stimulation; hr; hour; VN: vagus nerve; Hypoth: hypothalamus; Hz: Hertz; mA: milliamps; sec: seconds; min: minutes; μ S: microseconds; V: volts; sec: seconds; hr: hour; μ A: microamps; msec: milliseconds

Table 2.5 (continued) Neuromodulation studies assessing food intake and/or weight in animals

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Brown et al (1984)	6	Dogs	DBS	RCT i) vmH on/off vs. ii) subcortical white matter (control)	vmH white matter (control)	50Hz, 100µA, 3.5V 1.0msec a) deprived food for 24hrs, DBS for 1 hour, repeated with inactive, b) 1 hr of DBS every 12 hours for 3 days	a) dogs receiving DBS delayed their next meal despite food deprivation, whereas non-stimulated dogs resumed eating immediately. Control subcortical white matter controls resumed eating immediately in both on/off DBS. b) vmH DBS decreased average daily food & water intake. No influence with DBS to subcortical white matter.	
Stenger et al (1991)	10	Rats	DBS	3 conditions: i) vmH stimulated, ii) extra vmH stimulated, iii) vmH implanted controls	vmH	50Hz, 300µA, 100µs 20 trains of 60sec, 400ms on/ 600ms off, 12 sessions	Significant reduction in weight gain in vmH stimulated group compared to both controls.	
Bielajew et al (1994)	49	Rats	EBS (DBS)	2 conditions: i) vmH, ii) adjacent areas of vmH	vmH	50Hz, 300µA, 20 trains of 60s 400ms on/600ms off, 3hrs duration 3 sessions	Stimulation bound activity associated with decrease in weight gain & food intake. Weight gain & food intake not affected by electrode placement.	
Ruffin et al (1999)	8	Rats	EBS (DBS)	RCT crossover design i) active vs., ii) sham	vmH	20-25µA, 1ms pulse, 9ms interval 30sec on/30s off, 15min	vmH suppressed feeding & increased metabolism. No change with sham.	
Lehmkuhle et al (2010)	35	Rats	DBS	i) chronic stimulation vs. ii) 4 control groups	vmH	150Hz or 500Hz 10µA, 250µs pulses 6 weeks	Stimulated animals gained weight at a lower rate than controls. No significant difference in food intake between groups.	Weight gain altered without affecting feeding behaviours.

DBS/EBS: deep/electrical brain stimulation; RCT: randomised control trial; vmH; ventromedial hypothalamus; Hz: Hertz; µA: microamps; msec: V: volts; milliseconds; hr(s): hour(s); sec: seconds; µs: microseconds

**Chapter 3. A randomised single-session sham-controlled trial
of repetitive transcranial magnetic stimulation in anorexia
nervosa**

Introduction

Anorexia Nervosa (AN) is a severe, difficult to treat and life-threatening psychiatric illness. There is no recommended treatment for adult AN (NICE, 2004) and over 20% of individuals go on to develop severe and enduring forms of the illness, lasting 10-15 years (Schmidt et al., 2012; Steinhausen, 2002; Zipfel, Löwe, Reas, Deter, & Herzog, 2000). There is uncertainty about the management of these particularly chronic cases of AN (Hay et al., 2012). Talking therapies, which target thoughts and behaviours, have limited efficacy and there is a lack of evidence and acceptability of pharmacotherapy in AN (Mitchell, Roerig, & Steffen, 2013; Tortorella et al., 2014).

Emerging neural models of AN suggest a neuro-circuitry underpinning the illness – arising from alterations in ‘bottom-up’ limbic drives responsible for fear and emotional responses, in conjunction with aberrant ‘top-down’ frontal activity central to decision making processes and self-regulatory control (see Chapter 1; Friederich et al., 2013; Kaye et al., 2009; Lipsman et al., 2014; Marsh, Maia, et al., 2009). Given the need for novel treatments and the growing neuroimaging data in AN, advances in the understanding and treatment of AN are likely to arise from investigations which utilise neuroscience technologies that can both probe disease mechanisms whilst also exploring the therapeutic efficacy of novel treatment interventions (Insel & Gogtay, 2014; Schmidt & Campbell, 2013).

Neuromodulation research within psychiatric disorders is exemplary of this suggestion by the NIMH. The ability to alter neural activity will promote understanding of the neurophysiological underpinnings of mental illnesses, whilst also establishing the therapeutic potential of innovative treatment options. The therapeutic efficacy of the non-invasive neuromodulatory tool rTMS in other neuro-circuit psychiatric disorders such as depression, is relatively well established (Gaynes et al., 2014). Similarly, research into the biomarkers of response to rTMS has contributed to understanding the pathogenesis of depression, e.g. identifying the key role of substrates such as BDNF (Fidalgo et al., 2014).

Whilst preliminary data on the therapeutic utility of rTMS in AN are encouraging, further investigations in larger RCT that employ both symptom improvement and neurobiological outcomes are warranted. Therefore, the rTMS research described in this chapter assesses the effects of rTMS on some of the core symptoms of AN and in addition, examines the effects of rTMS on food preference/consumption and stress responses in AN. Moreover, issues such as cortical excitability in AN are discussed, along with safety and tolerability considerations in relation to the use of rTMS in AN.

This chapter outlines a single-session, randomised controlled trial (RCT) of either real/sham (placebo) rTMS in AN and is reported according to the following structure;

Background and Methods

- Chapter 3.1 Introduction and explanation of rTMS
- Chapter 3.2 Outline of the RCT of rTMS in AN

Results

- Chapter 3.3 The effects of rTMS on the core symptoms of AN
- Chapter 3.4 The effects of rTMS on food preference and consumption in AN
- Chapter 3.5 The effects of rTMS on salivary cortisol concentrations in AN
- Chapter 3.6 Cortical excitability in AN
- Chapter 3.7 Safety, tolerability and acceptability of rTMS in AN

Summary

- Chapter 3.8 Overall summary

Chapter 3.1 Repetitive Transcranial Magnetic Stimulation

TMS is a form of non-invasive neuromodulation first developed in 1985 by Anthony Barker and his colleagues at the University of Sheffield. In the initial report, this group demonstrated the induction of a motor evoked potential (MEP) by applying a TMS pulse over the motor cortex and activating the contralateral thumb muscle (Barker et al., 1985). Most knowledge on TMS comes from studies on motor conductivity, given that single-pulse TMS to the motor cortex produces obvious, measurable effects i.e. bursts of muscular activity that can last for 5-10 milliseconds (Ridding & Rothwell, 2007).

Continuing progress in the development of TMS protocols led to a number of ways in which TMS pulses can be applied. Paired-pulse TMS involves two stimuli separated by an inter-stimulus interval and can be used to measure intracortical facilitation/inhibition, interhemispheric inhibition and cortico-cortical interactions (see Chapter 3.6 for more details or Rossi et al., 2009). Delivery of multiple single pulses, repeated within a short period, is known as repetitive TMS or rTMS. The ability of rTMS to induce sustained cortical effects (up to 30-60 minutes) that lead to physiological and cognitive effects (Pascual-Leone et al., 1998; Pascual-Leone, Valls-Sole, Wassermann, & Hallett, 1994; Ridding & Rothwell, 2007) encouraged research into its therapeutic utility in a range of neurological and psychiatric disorders (Horvath, Perez, Forrow, Fregni, & Pascual-Leone, 2011).

The first proof-of-principle study of rTMS in depression was conducted almost 20 years ago (Kolbinger, Höflich, Hufnagel, Müller, & Kasper, 1995). Since then, there has been a dramatic increase in the number of published rTMS studies worldwide, both within healthy individuals and patients with various neurological and psychiatric conditions (Rossi et al., 2009). To guide such research, and in response to growing ethical and safety concerns, expert consensus groups regularly update guidelines for the use of rTMS in both research and clinical settings (Lefaucheur et al., 2014; Rossi et al., 2009; Wassermann & Lisanby, 2001). Adhering to such recommendations, rTMS has been established as a safe technique (Loo, McFarquhar, & Mitchell, 2008) and

large multi-centre controlled trials demonstrating its therapeutic efficacy have lead to FDA approval of rTMS as a second-line treatment for depression (Gaynes et al., 2014; George et al., 2010; O'Reardon et al., 2007).

Mechanisms

Physics

The science underpinning TMS is based on Faraday's law of electromagnetic induction. Passing an electrical current through two loops of a wire coil generates a time-varying magnetic field that induces a secondary electrical current – whose magnitude is proportional to the rate of change of the magnetic field – in a nearby conductor, including human tissue. In terms of TMS, as the electrical current passes through the coil, a magnetic field similar to that of a conventional MRI scanner (1.5-2.0 Tesla), but much shorter in duration, is produced (Rossi et al., 2009). When the TMS coil is held against an individual's head, the magnetic field passes through the scalp and skull to induce a secondary electrical current (lasting about 200 μ s) in the brain (see Figure 3.1 panel a).

Given that the magnetic field rapidly falls off with distance from the coil, the stimulation is thought to primarily activate neural elements in the cortex or subcortical white matter. The induced electric field causes ions to flow in the brain and alters the electric potential of cell membranes, depolarising and hyperpolarising both local neurones in the cortex beneath the coil, and axons that project from the site of stimulation (Rossi et al., 2009). The electric field in the cortex is approximately 150 V/m and varies in depth and focality depending on the type of TMS coil used. Various physiological and behavioural effects result, depending on the TMS protocol used and the brain areas targeted (Horvath et al., 2011; Ridding & Rothwell, 2007). In summary, TMS non-invasively stimulates the brain via electromagnetic induction, inducing neurophysiological changes that facilitate cognitive and behavioural changes.

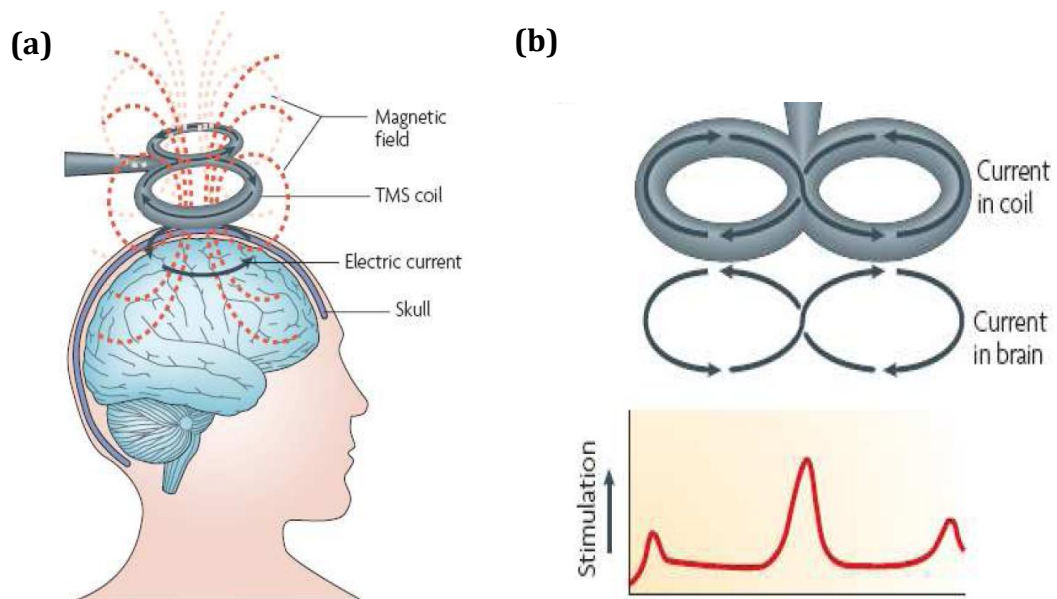


Figure 3.1 Diagram of the (a) application and (b) magnetic fields of TMS

Panel (a) demonstrates how TMS is applied, the magnetic field and secondary electrical current induced in the brain. Panel (b) illustrates the opposing direction of currents within the coil and the resulting magnetic field, which has a peak area of stimulation directly under the central junction of coil. Reprinted as appears in Ridding & Rothwell (2007) with permission from Nature Publishing Group.

Coil types

Single circular coils were the simplest and first TMS coils to be used. They induce a circular current flow under the coil, provide good depth of penetration (up to 3.5cm) but they are limited by poor focality (34cm^2). When two circular coils are placed side by side, the induced electrical field is maximised at the junction of the two coils (see Figure 3.1 panel b) and this figure-of-eight coil design is most commonly used as it allows a good focality (5cm^2) to depth (3.4cm) ‘trade-off’ (Deng, Lisanby, & Peterchev, 2013; Epstein, 2008). More recently, an H-coil has been developed that can alter neural activity up to a depth of 6cm and therefore may be able to modulate deeper, limbic brain structures. Preliminary investigations utilising the H-coil within psychiatric disorders, albeit predominantly to prefrontal regions, have demonstrated promising results (Bersani et al., 2013; Rossi et al., 2009).

In controlled trials of rTMS, a convincing method of placebo stimulation is required. Sham rTMS procedures aim to mimic the experience (i.e. appearance, noise, sensation) of real rTMS. Some sham procedures involve holding a real rTMS coil on an angle in order to reduce conductivity, however, this method still produces substantial stimulation (Lisanby, Gutman, Luber, Schroeder, & Sackeim, 2001). Therefore, specialised sham coils in which the windings are arranged within the coil to reduce or remove electrical current are now most commonly used in controlled trials. However, most sham coils do not adequately replicate the sensation of real rTMS. Improved designs with integrated scalp electrodes that produce stronger tactile responses aim to overcome this problem, however, they are typically cumbersome to use (Epstein, 2008).

Given the difficulties in mimicking real rTMS, robust crossover designs are difficult to implement successfully and thus, parallel rTMS study designs are most common. 'Blinding' success, which is the ability to keep subjects and/or researchers unaware of the intervention administered, is crucial in interpreting the effects of rTMS, yet is seldom reported. However, recent reviews and meta-analyses of those that do, suggest satisfactory rates of blinding, reporting that around half of participants are unable to guess whether they had real or sham rTMS (Berlim, Broadbent, & Van den Eynde, 2013; Broadbent et al., 2011).

Terminology

Motor threshold and stimulation intensity

The intensity at which rTMS is typically applied depends on cortical excitability which varies between individuals. This is established by applying TMS to the motor cortex to establish a person's motor threshold (MT). Typically this is the resting MT, i.e. when the target muscle is relaxed. The MT can be determined in two ways: the observed method where MT is the minimum stimulator output intensity required to evoke 5 out of 10 visible movements or twitches in a contralateral muscle, typically the thumb/finger. Alternatively, MT can be established using MEP whereby MT is the minimum stimulator output intensity required to obtain 5 out of 10 MEP greater than 50 μ V (Rossini et al., 1994;

Rothwell et al., 1999). There is a general consensus that the MEP method is a more accurate, conservative and safer way to assess MT, and is therefore preferable to the observed movement method (Anderson & George, 2009; Hanajima et al., 2007; Rossi et al., 2009).

Each person's MT should be determined prior to rTMS and stimulation output/intensity, i.e. the intensity of the magnetic field, is based on MT. Typical stimulation intensities used within psychiatric research, range between 80 – 120% of MT (George et al., 1995; O'Reardon et al., 2007) with some evidence suggesting higher stimulation intensities are associated with greater treatment efficacy (Padberg et al., 2002).

Pulse frequency and trains of stimulation

In rTMS protocols, the number of pulses delivered per second is referred to as the frequency (Hz) of the stimulation. LF or 'slow' rTMS refers to protocols with a stimulus rate less than 5Hz, whilst HF or 'fast' rTMS applies pulses at a rate of 5Hz or above (see Figure 3.2). The two types of rTMS, LF and HF, are proposed to have inhibitory and excitatory effects on neural activity respectively (Rossi et al., 2009); the neurophysiological mechanisms of which are described below.

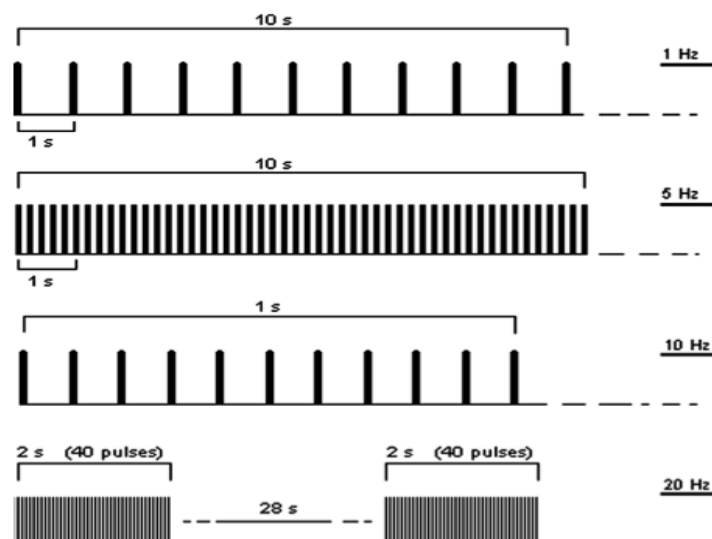


Figure 3.2 Examples of rTMS protocols

10 seconds of 1Hz/LF; 10 seconds of 5Hz/HF; 1 second of 10Hz/HF and 20 Hz rTMS delivered in 2 second train/28 second inter-train intervals. Reprinted (with minor amendment) as appears in Rossi et al. (2009) with permission from Elsevier.

For both safety and efficacy reasons, current guidelines suggest LF rTMS should be applied in a continuous train, whilst the pulses of rTMS in HF protocols should be administered in 'trains' of stimulation separated by adequate 'inter-train intervals' of no stimulation (see last example in Figure 3.2). This is done for a number of reasons, but primarily to ensure safety, as the accumulation of rTMS pulses in the brain increases risk of seizure. Also, the electrical pulses cause heating of the TMS device and the inter-train interval allows time for both the TMS device and coil to cool in between trains.

Physiological effects

Despite significant advances in the development of rTMS devices and protocols, our understanding of the neurophysiological mechanisms underlying its effects is limited. Short-term effects are proposed to reflect changes in neural excitability caused by shifts in the ionic balance in populations of active neurones (Ridding & Rothwell, 2007). Long-term effects of rTMS on neural activity have been proposed to result from a number of mechanisms. Following rTMS, changes in cerebral blood flow (CBF) (Loo et al., 2003) and the release of dopamine (Cho & Strafella, 2009), serotonin (Baeken et al., 2011) and glutamate (Michael et al., 2003) in both local and remote areas to the brain region targeted, have been reported. However, the most current hypothesis underlying the therapeutic mechanisms of rTMS within neuro-circuit based disorders relates to changes in the 'effectiveness' and functional remodelling of neuronal synapses, referred to as neuroplasticity (Medina & Tunes, 2013). For example, there is a growing understanding of the association between rTMS and the expression of BDNF, a neurotrophin essential for synaptic and learning plasticity (Gersner et al., 2011; Medina & Tunes, 2013) along with reported increases in glutamatergic synaptic strength inducing structural plasticity and functional network connectivity following HF rTMS (Esslinger et al., 2014; Vlachos et al., 2012). Thus, the enhancement or reduction of synaptic transmission that characterises long-term potentiation (LTP) and long-term depression (LTD) respectively, have been proposed to underlie the effects of rTMS (Hoogendam, Ramakers, & Di Lazzaro, 2010).

Excitatory and inhibitory effects of rTMS

The LTP/LTD effects of rTMS depend on the protocol used; HF rTMS typically excites neural activity whilst LF inhibits (Houdayer et al., 2008). For example, increases and decreases in rCBF of the PFC in depressed patients have been reported following HF and LF rTMS respectively (Loo et al., 2003). In healthy individuals, HF rTMS reportedly increases concentration of dopamine (Cho & Strafella, 2009; Strafella, Paus, Fraraccio, & Dagher, 2003) and serotonin concentrations in depressed patients (Baeken et al., 2011). Moreover, animal studies suggest that levels of BDNF are increased following HF rTMS, yet remain unchanged following LF rTMS (Gersner et al., 2011). Such findings underscore the notion that HF and LF rTMS have opposite effects on neural activity (Houdayer et al., 2008). However, frequency is not the only determinant of the neural effects of rTMS, as longer stimulation duration and inter-individual variability are also relevant when considering the neural excitatory, inhibitory or neuroplasticity effects of rTMS (Hoogendam et al., 2010).

Stimulation site and their localisation

The site of stimulation in rTMS research depends on the condition and/or symptom of interest. The primary area targeted in psychiatric research has been the DLPFC. Specially, the DLPFC has been targeted with rTMS in depression for a number of reasons including suggested dysfunction (specifically an underactive left DLPFC), frontal asymmetry, the DLPFC being highly connected with other key mood regulation regions, but also because of its accessibility for rTMS (Cummings, 1993; Wassermann & Lisanby, 2001).

A large number of studies have located the DLPFC using the '5cm anterior method' in which it is located by measuring and positioning the coil 5cm anterior from the optimal point/'hot-spot' for determining MT. However, recent evidence suggests that more specific stereotaxic localisation methods based on individual neuroimaging should be used. This type of MRI-guided rTMS, termed 'neuronavigation', has been suggested to be superior in accurately and reliably (both between and within individuals) locating the DLPFC when compared to the 5cm anterior method (Ahdab, Ayache, Goujon, & Lefaucheur, 2010;

Bradfield, Reutens, Chen, & Wood, 2012; Herwig, Padberg, Unger, Spitzer, & Schönfeldt-Lecuona, 2001; Herwig, Schönfeldt-Lecuona, et al., 2001; Rusjan et al., 2010). Moreover, preliminary evidence suggests that, compared to rTMS applied via the 5cm anterior method, neuronavigated rTMS elicits greater therapeutic response in depression (Fitzgerald et al., 2009), but more studies are required to confirm this important finding.

The use of repetitive transcranial magnetic stimulation within psychiatry

As has been discussed, the ability of rTMS to induce long-lasting neural changes that influence cognitions and behaviours has enabled investigations in psychiatric disorders. The literature surrounding the use of rTMS in depression is the most abundant, with comprehensive meta-analyses supporting its therapeutic efficacy in treatment resistant patients (Gaynes et al., 2014; Slotema et al., 2010). Similarly, recent meta-analyses also support the efficacy of rTMS in schizophrenia (Hovington, McGirr, Lepage, & Berlim, 2013) and obsessive compulsive disorder (Berlim, Neufeld, & Van den Eynde, 2013). There is also increasing interest in the use of rTMS in treating drug and alcohol addiction (Bellamoli et al., 2014), and on its effects on eating behaviours and/or body weight as these have and implications for the treatment of eating disorders (see Chapter 2 or McClelland, Bozhilova, Campbell, & Schmidt, 2013; Van den Eynde & Guillaume, 2013). Undoubtedly, a better understanding of the physiological effects of rTMS and the neural underpinnings of the conditions treated with rTMS will facilitate establishing its therapeutic potential within psychiatry (Ridding & Rothwell, 2007; Wassermann & Lisanby, 2001).

Chapter 3.2 Outline of the study

This chapter describes the first part of the research involving rTMS in AN (in this thesis) and consists of a proof-of-concept, single-session RCT of real versus sham HF neuronavigated rTMS to the left DLPFC. It follows the recent recommendations of Brunoni and Fregni (2011) for clinical trials involving non-invasive neuromodulation, namely, a priori sample size estimation, definition of primary outcomes and statistical analysis prior to the start of the study, strict eligibility criteria, a stratified randomisation procedure and the exploration of potential biomarkers of response.

The primary aim was to examine the short-term effects of rTMS on core symptoms of AN (Chapter 3.3). Additionally, the effects of rTMS on food preferences and food consumption in AN were investigated (Chapter 3.4), along with the physiological effects of rTMS on salivary cortisol (Chapter 3.5). Cortical excitability in AN is discussed (Chapter 3.6) together with the safety, tolerability and acceptability of rTMS in AN (Chapter 3.7). Individual hypotheses, results, limitations and implications of the research are discussed in each section and then a summary of the effects of rTMS in AN is provided (Chapter 3.8).

Participants

A sample size calculation based on previous studies (Uher, Yoganathan, et al., 2005; Van den Eynde et al., 2010) and including a 5% drop out rate, indicated that 32 individuals per group were needed to detect an effect size of $d = 0.90$ with 80% power using two-sided t-tests with $p = 0.05$. Therefore, a total of 64 participants were needed. 68 participants (1 male) were recruited who were over 18 years of age and who had a current DSM-5 diagnosis of AN. This was achieved via recruitment from the Eating Disorders outpatients department at the Maudsley Hospital (South London and Maudsley NHS Foundation Trust), by email advertisement throughout King's College London and via the national eating disorder charity website (www.b-eat.co.uk).

Diagnosis was established via the referring clinician and/or the Eating Disorder Diagnostic Scale (EDDS) (Stice, Telch, & Rizvi, 2000). Principal inclusion criteria

were a BMI of 14 – 18.5 kg/m². Contra-indications to both the MRI scan and the rTMS were checked with the King's College London, Centre for Neuroimaging Sciences standard MRI Safety Questionnaire (Appendix E.4) and the TMS Adult Safety Screen Questionnaire (Appendix E.5) (Keel, Smith, & Wassermann, 2001) respectively. Exclusion criteria were: left-handedness, a BMI less than 14, or more than 18.5 kg/m², being on a dose of psychotropic medication that had not been stable for at least 14 days prior to enrolment, pregnancy, personal/family history of seizures and/or epilepsy and excessive alcohol consumption (drinking >3 units per day on a daily basis) (NHS, 2013) and/or excessive nicotine use (>15 cigarettes/day). Local ethical committee approval was obtained (ref: 12/LO/1525) and the trial was registered prior to commencement (www.controlled-trials.com registration number: IRCTN22851337). Written informed consent was obtained from all participants. The participant information sheet and consent form are included in Appendices C.1 and D.1 respectively.

Randomisation and blinding

A CONSORT diagram (Schulz, Altman, & Moher, 2010) of the recruitment and randomisation procedure is presented in Figure 3.3. The randomisation was set up and conducted by an independent researcher to ensure allocation concealment. The computer programme Stata (version 11.0 for Windows) was used to randomise participants, stratified by AN subtype diagnosis (restrictive or binge/purge), in a random block size design using block sizes of 2, 4, 6, 8. Following screening/baseline(1) assessments, once participants were deemed eligible and consented to taking part, they were randomised. Due to a small delay between baseline(1) and booking the MRI scan/testing session, several participants ($n = 9$) withdrew post-randomisation for various reasons e.g. feeling unwell. Therefore, a total of 51 female participants attended, intending to complete the full protocol.

Three researchers were involved in the experiments: one who delivered the rTMS (the candidate), one who helped with the rTMS and neuronavigation equipment, and the other who administered the pre- and post-rTMS tasks. The

latter researcher was blind to the experimental condition (real or sham rTMS). Participants were not informed about which condition they were randomised to until after their data collection was complete, which was at the end of their 24 hour follow-up phone call.

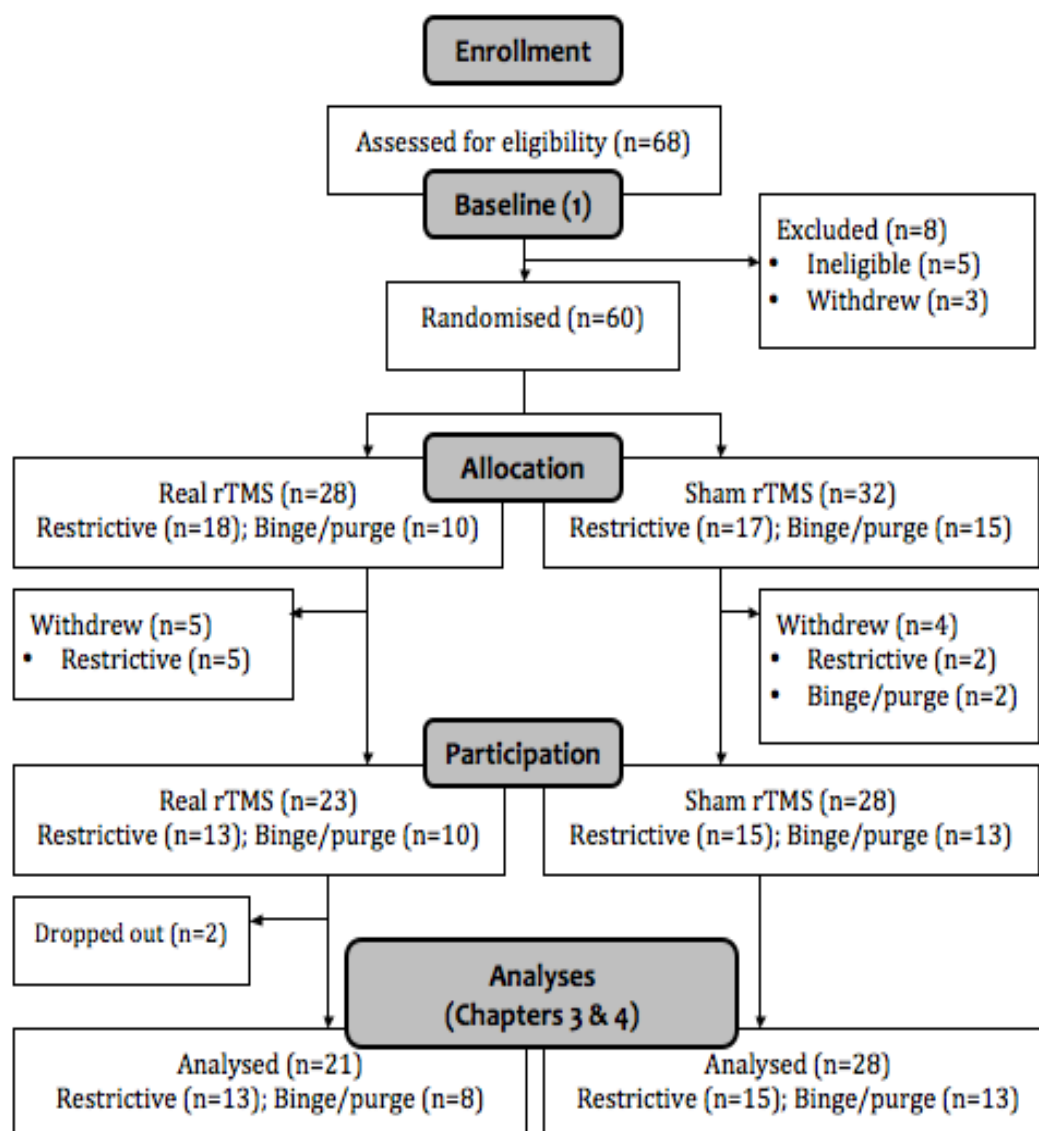


Figure 3.3 CONSORT diagram of recruitment and randomisation procedures

Protocol

A standard operating procedure was developed for the RCT of rTMS in AN and applies to Chapters 3 and 4. Table 3.1 provides a schematic presentation of the procedures followed.

Following baseline(1) and randomisation, study procedures were typically completed in one day; however, some participants had their MRI scan and the rTMS session split over two days. To use neuronavigated (MRI-guided) rTMS, participants initially underwent a structural MRI scan. This was used with Brainsight® to neuronavigate the rTMS coil to the left DLPFC (more details of this procedure to follow). When procedures were done on the same day, participants had a 2 hour break between the scan and testing (to allow the MRI to be uploaded on neuronavigation software). Participants were instructed to refrain from eating for at least 1 hour prior to the testing session.

The various data collection time points (TP) are illustrated in Table 3.1. At the start of the testing session (Baseline 2 or TP1) information on ED symptoms and mood was collected using the Eating Disorder Examination Questionnaire (EDE-Q version 16) (Fairburn, 2009) and the Depression Anxiety and Stress scale (DASS-21) (Lovibond & Lovibond, 1995a) which are included in appendices F1 and F.2. The first of five saliva samples (S1) collected via Salivettes® was obtained, along with baseline blood pressure (BP) and pulse. 'Initial' 10cm visual analogue scales (VAS) on urge to restrict, levels of feeling full, feeling fat, urge to exercise, levels of stress and anxiety were administered (Appendix G.1). A monetary temporal discounting (TD) task (TDpre) was then completed (see Chapter 4 for more details).

Table 3.1 Study protocol for the RCT of rTMS in AN.

	Time point (TP)	Tasks/Assessments	Researcher
<div><div></div><div>±2 hr</div></div>	Screening/ Baseline(1)	Inclusion/exclusion criteria, TMS safety questionnaire, demographic & ED/psychiatric information (EDDS/SCID)	Blinded
	MRI	MRI safety questionnaire, MRI scan	
	~2hr BREAK (no eating 1 hour prior to next stage of testing)		
	Baseline(2)/ TP1	EDE-Q & DASS-21 Saliva (S1) Blood pressure (BP) & pulse	Unblinded
		Initial VAS Temporal discounting task (TDpre) ²	Blinded
	Food Challenge Task (FCTpre)		
	TP2	Food, initial & additional VAS Saliva (S2)	
	Standard rTMS description read by participants Motor Threshold (MT), BP & pulse REAL/SHAM rTMS BP & pulse Discomfort VAS		Unblinded
		Saliva (S3) Temporal discounting task (TDpost)	Blinded
	Food Challenge Task (FCTpost)		
	TP3	Food, initial & additional VAS Saliva (S4) Discomfort/side effects	Blinded
	TP4	Initial VAS, Saliva (S5) Smoothie task BP & pulse Height & weight measured	
	TP5 24hr call	Initial VAS Acceptability as a treatment Blinding assessment	Unblinded

EDDS: eating disorder diagnostic scale; SCID: structure clinical interview for diagnosis of DSM-IV disorders; MRI, magnetic resonance imaging; EDE-Q: eating disorder examination questionnaire; DASS-21: depression, anxiety and stress scale (21 item); VAS; visual analogue scale.

² The TD task requires detailed introduction and explanation. Therefore, it is reported in the subsequent chapter (Chapter 4), however, the study design and protocol is the same in both Chapter 3 and 4.

The first delivery of our food challenge task (FCTpre) (Van den Eynde, Guillaume, et al., 2013) was then administered: this task required participants to watch a 2 minute film of people eating highly palatable foods (chocolate, nuts, crisps, biscuits) while the same foods were in the room. At this point (TP2), 'food-related' VAS regarding the perceived smell, taste, appearance and urge to eat each food type were completed (Appendix G.3), along with the initial VAS and 'additional' VAS regarding related psychopathologies (mood, calmness, hunger, urge to eat, urge to binge eat and urge to be sick or purge; Appendix G.2). A second saliva sample (S2) was also collected.

Following the above, a standardised information sheet about the rTMS procedure (though no information which could reveal their sham/real allocation) was given to participants to read immediately before the rTMS component of the session (this is provided in Appendix I.1). Participants were allowed to ask any questions they might have at that point. A real rTMS figure-of-eight coil and the Brainsight® neuronavigation equipment were then calibrated to the individual. The Magstim® Rapid device (Magstim®, UK) was used to establish each participant's MT. Following MT measurement, BP and pulse were recorded. The rTMS coil was then changed to either a real/sham rTMS coil and recalibrated with Brainsight®. This was then used with the Magstim® device to administer real/sham rTMS³. Immediately after the final, twentieth rTMS train, BP and pulse were recorded and a third saliva sample was collected (S3). Participants also completed a 10cm VAS on the 'discomfort' they experienced during the rTMS session.

After real/sham rTMS the TD task was re-administered (TDpost), followed by the FCTpost. Food related, initial and additional VAS were then collected (TP3), followed by a fourth saliva sample (S4). Any current pain/discomfort were then assessed and discussed. Towards the end of the session, the initial VAS were repeated (TP4) and a final saliva sample (S5) was collected. At this point, participants were asked to choose one of three smoothie flavours and to drink as much as possible. Following this, BP and pulse were recorded and

³ More details on the methods used to establish MT and the delivery of rTMS is given in the 'Procedures' section of this chapter.

measurements of height and weight were taken. Participants were telephoned the next day for a 24 hour follow-up (TP5) during which the initial VAS were repeated, adverse events were discussed and participants were asked, if rTMS proved efficacious in AN, whether they would consider it as a treatment (a session each week day for four weeks). Finally, allocation concealment/blinding was assessed, and then revealed.

Procedures

Apart from the structural MRI scan, which was done in the Centre for Neuroimaging Sciences, all the study procedures took place in the TMS lab at the Institute of Psychiatry, Psychology and Neuroscience, King's College London.

MRI and neuronavigation

All participants underwent a structural MRI scan, which was used with Brainsight® to neuronavigate the TMS coil to the left DLPFC. The imaging protocol included a high-resolution sagittal 3D T1-weighted Magnetisation Prepared Rapid Gradient Echo (MPRAGE) volume (voxel size 1.1 x 1.1 x 1.2 mm³) which was obtained using a customised pulse sequence (Jack et al., 2008). Full brain and skull coverage was required and detailed quality control was carried out on all MRI data according to a previously described quality control procedure (Simmons et al., 2009, 2011).

Following the MRI scan and prior to the main rTMS session, MRI images were uploaded to Brainsight®. This involved calibrating the structural MRI scan to the Brainsight software (personal instructions for this procedure are included in Appendix I.2). The site for the left DLPFC was obtained by inputting pre-determined Talairach co-ordinates of $x = -45$, $y = 45$, $z = 35$. These values were adopted from Fitzgerald et al. (2009) who demonstrated a greater therapeutic effect in depressed patients using these co-ordinates (in comparison to the 5cm anterior method).

Following importation of the MRI scan into Brainsight, the software was calibrated to the TMS coil in use and to the individual. This was done after the

pre-rTMS assessments and immediately before the MT/rTMS component of the protocol. The TMS coil was calibrated to the software using a 'calibration block'. To calibrate participants to the Brainsight software, individuals wore a headband, termed 'subject tracker', whilst a calibrated 'pointer' was held against four landmarks; the nasion, nose tip and left and right tragus.

Motor threshold

Following calibration, the Magstim Rapid device (Magstim, Whitland, Wales, United Kingdom), using a real rTMS figure-of-eight coil, was used to establish participants' resting MT. The left M1 and optimum spot in the left M1 to activate the first dorsal interosseous (FDI) muscle was located on the Brainsight software (by eye, i.e. not using imaging co-ordinates) and the participant's MT was defined as the minimum stimulus required to evoke 5 out of 10 MEP greater than 50 μ V. This was conducted according to the 'lower threshold' method – starting at 40% of stimulator output and increasing in increments of 5 until 5 out of 10 responses were greater than 50 μ V (Rossini et al., 1994; Rothwell et al., 1999) and was identical across both groups (real and sham rTMS), that is, all participants' MT were determined using a real TMS coil.

Repetitive transcranial magnetic stimulation procedure

After MT was determined, the real rTMS coil used to establish MT was changed in both groups. The same Magstim Rapid device with either a real or sham figure-of-eight coil was used for the rTMS. The device used to administer rTMS had a peak discharge current of 7000 Amps and peak discharge voltage of 2000 Volts, producing a sine wave magnetic field with a peak strength of 2 Tesla in a 250 μ s pulse.

The real or sham rTMS was delivered according to our previous protocols (Van den Eynde, Guillaume, et al., 2013); **20 x 5 second trains with 55 second inter-train intervals, at a frequency of 10 Hz and intensity of 110% of the individuals MT, providing 1000 pulses over 20 minutes.** Sham stimulation was given at the same location and using the same protocol. These parameters (frequency, intensity, duration of the trains, inter-train time, and total number

of pulses delivered) are in accordance with the current rTMS safety guidelines (Rossi et al., 2009). The researcher (PhD candidate) who delivered the rTMS, was trained in delivery of both rTMS and tDCS at the Berenson-Allen centre of non-invasive brain stimulation, Harvard Medical School, Boston, USA.

Food challenge task

Evidence supports the importance of context-dependent neural activity on outcome of rTMS (Gersner et al., 2011). Therefore, rTMS was combined with a food-cue exposure task in order to provoke and induce ED related psychopathology and thus bolster the effects of rTMS on these symptoms. The exposure FCT task, was completed both immediately before (FCTpre) and after (FCTpost) either real/sham rTMS. Participants were shown a 2-minute video of people eating highly palatable foods (chocolates, crisps, biscuits and nuts). Instructions for this task and screen shots of the video are presented in illustrated in Appendix H.1. These same foods were simultaneously present in the room. They were asked to watch the video and then rate these foods on their perceived smell, taste, appearance and desire to eat these foods using 10cm VAS (included in Appendix G.3). They were not required to eat or touch the foods.

Chapter 3.3 The effect of repetitive transcranial magnetic stimulation on symptoms of anorexia nervosa

As described in Chapter 1, AN is a severe and life-threatening mental illness. In adults, the best available psychotherapies have limited remission rates (Zipfel et al., 2000) whilst the use of pharmacotherapy in AN is not empirically supported and has low acceptability (Mitchell et al., 2013). Emerging neuroimaging data implicate altered 'bottom-up' processing in limbic structures (such as the insula and amygdala), in conjunction with aberrant 'top-down' cognitive control mechanisms (involving the PFC), suggesting a neuro-circuitry underpinning to AN (Kaye et al., 2009; Park et al., 2014; van Kuyck et al., 2009). Given the somewhat limited efficacy of existing talking psychotherapies and the emerging knowledge of neural underpinnings of AN, a strong case can be made for developing brain-directed treatments (Schmidt & Campbell, 2013). This is in accordance with recommendations by the NIMH for progressing the understanding and treatment of psychiatric disorders via the use of neuroscience technologies (Insel & Gogtay, 2014).

The neuromodulation technique rTMS non-invasively alters neural activity and has demonstrated therapeutic effects in psychiatric disorders such as depression and addiction (Gaynes et al., 2014; Jansen et al., 2013; Slotema et al., 2010). More specifically, neurocircuit-based models of addictive disorders implicate specific brain networks at different stages of addiction. Thus, the ventral tegmental area (VTA) and ventral striatum are proposed to be involved in initial binge/intoxication periods, whilst the amygdala is proposed to underlie the withdrawal/negative affect stage and prefrontal regions are implicated in the preoccupation and anticipation stages of addiction (Koob & Volkow, 2010). A number of mechanisms have been proposed to support the use of rTMS in addictive disorders. Given interconnections between the DLPFC and VTA, rTMS may increase dopamine transmission, and this notion has been supported in both human and animal studies (Diana, 2011; Keck et al., 2002; Strafella et al., 2003). Additionally, given altered activity in prefrontal regions (Goldstein & Volkow, 2011) and poor inhibitory control (Perry & Carroll, 2008) often reported in relation to addictive disorders, rTMS applied to the DLPFC

may improve cognitive control mechanisms. Given such models and mechanistic hypotheses, a number of studies have explored the utility of rTMS applied to the DLPFC within addictive disorders and a recent meta-analysis demonstrated moderate effects for the reduction of cravings (Jansen et al., 2013). Given that there are some shared neural underpinnings in responses to drug and food cues (Tang, Fellows, Small, & Dagher, 2012), our group initiated research on the effects of rTMS on food cravings. In frequent food cravers, real rTMS was shown to prevent cravings during food-cue exposure and sham rTMS increased cravings (Uher, Yoganathan, et al., 2005). Whilst another study involving a more sophisticated sham rTMS technique suggested no effects of rTMS on food cravings (Barth et al., 2011), other studies investigated the potential of tDCS (a similar form of non-invasive neuromodulation) and have reported reductions in food cravings (Fregni et al., 2008; Goldman et al., 2011; Kekic et al., 2014).

Given that food cravings and consequential binge-eating episodes are a characteristic of BN, interest in the effects of rTMS on BN symptoms arose. Individual case reports support the therapeutic potential of rTMS in BN (Downar et al., 2012; Hausmann et al., 2004). However, whilst the only multiple session (5 daily sessions a week for 3 weeks) RCT of real/sham rTMS in an ED sample reported improvements in BN symptoms (i.e. bingeing and vomiting behaviours), there were no significant differences between real/sham groups (Walpoth et al., 2008). This study may have been underpowered ($n = 14$) or, given the typical 20 rTMS session protocols used in the treatment of depression, it may have administered too few rTMS sessions. Since then, our group conducted a single-session RCT and demonstrated that real versus sham rTMS temporarily reduced the urge to eat and subsequent binge eating episodes in patients with BN (Van den Eynde et al., 2010).

Along with the growing understanding of the neuro-circuitry associated with AN (Kaye et al., 2009; van Kuyck et al., 2009), these aforementioned improvements in ED related symptoms following rTMS and findings of improved symptoms and weight gain following 20 sessions of rTMS in an individual with AN (Kamolz et al., 2008) increased our interest in the therapeutic potential of rTMS in AN. Our group conducted a single-session pilot

study of rTMS in 10 individuals with AN and demonstrated that, following a food-cue exposure task, rTMS temporarily reduced levels of anxiety, feeling full and feeling fat, i.e. some of the core symptoms of AN (Van den Eynde, Guillaume, et al., 2013). Following this, we reported two cases of enduring AN (Chapter 5) which demonstrated sustained improvements in ED psychopathology and mood following 20 sessions of rTMS (McClelland, Bozhilova, Nestler, et al., 2013). Moreover, a recent pilot study in seven individuals with AN using a similar neuromodulation paradigm – ten sessions of left DLPFC tDCS – reported reductions in ED and depressive symptoms (Khedr, Elfetoh, Ali, & Noamany, 2014). Whilst the preliminary data regarding the therapeutic effects of non-invasive neuromodulation such as tDCS and rTMS in AN are encouraging, the small numbers and the lack of comparison control conditions limit findings. Thus, there is a need for an adequately powered RCT which compares the effects of real and sham rTMS on the symptoms of AN.

Moreover, an important aspect of rTMS study designs that is seldom reported is 'blinding' success. The placebo response to rTMS in depression is reportedly comparable to that found in pharmacological interventions (Brunoni, Lopes, Kaptchuk, & Fregni, 2009) and therefore the success of allocation concealment in an RCT of rTMS is crucial for interpreting results and generalising findings. Recently, reviews and meta-analyses have highlighted that most studies fail to report blinding success (Broadbent et al., 2011). In those that do, participants in real/sham groups do not significantly differ in their ability to correctly guess their intervention allocation (Berlim, Broadbent, et al., 2013): however, trends towards participants in the real group more often guessing correctly have been identified. Therefore, reporting and evaluating blinding success in RCT of rTMS is essential to provide a fair representation and interpretation of results.

The aim of the research reported in this chapter is to establish the short-term (up to 24 hours) effects of rTMS on symptoms of AN. Additionally, as this is a double-blind study, there is a responsibility to assess and report the success of allocation concealment in both participants and researchers. We hypothesised that real versus sham rTMS would temporarily reduce the core symptoms of AN. We also hypothesised that secondary outcomes regarding related

psychopathology (e.g. urge to eat, mood etc.) would also be improved following real rTMS. Finally, we predicted that both participants and researchers would be unable to guess correctly their intervention allocation at a rate better than chance (i.e. 50%).

Methods

Participants

Recruitment and randomisation procedure are described in Chapter 3.2.

Procedure

A description of the procedures is provided in Chapter 3.2.

Measures

Baseline measures

Eating disorder pathology

Eating Disorders Examination – Questionnaire version 6 (EDE-Q; see Appendix F.1): Based on the clinical interview version (Eating Disorder Examination; EDE) the Eating Disorders Examination Questionnaire (EDE-Q; Fairburn & Beglin, 1994) is a self-report measure assessing ED symptoms over the past month. Version 6 of the EDE-Q (Fairburn, 2009) was used in this study to provide information on core ED constructs and the frequency of ED behaviours (e.g. bingeing/purging). Questions relate to the past 28 days and are measured on a 7-point Likert scale ranging from zero (no days) to six (every day). The items represent various ED experiences which, when averaged, reflect the following constructs and subscales; restraint, eating concern, shape concern and weight concern. The mean of these four subscales provides a global EDE-Q score. High subscale and global scores indicate greater ED psychopathology, with a proposed clinical cut-off score of ≥ 4 (Carter, Stewart, & Fairburn, 2001; Luce, Crowther, & Pole, 2008; Mond, Hay, Rodgers, Owen, & Beumont, 2004). The frequency of ED behaviours (e.g. bingeing, vomiting, laxative use etc.) can also be established via answers/estimates of incidence over the past 28 days.

The EDE-Q has good reliability, validity and clinical utility (Berg, Peterson, Frazier, & Crow, 2012; Luce et al., 2008; Mond et al., 2004).

Other psychopathology

Depression, Anxiety and Stress Scale – short version (DASS-21; see Appendix F.2) (Lovibond & Lovibond, 1995a): The DASS-21 is a short version of a 42 item self-report measure (Lovibond & Lovibond, 1995a). The DASS-21 is comprised of items measured on a 4-point Likert scale ranging from 0 (did not apply to me at all) to 3 (applied to me very much, or most of the time) and assesses mood state over the past seven days. Each item loads on to one of three subscales, which when totalled provide scores for depression, anxiety and stress. High scores indicate worse symptomatology; severity ranges from normal-mild-moderate-severe-extremely severe are indicated by scores of 0-4, 5-6, 7-10, 11-13, 14+ for depression, 0-3, 4-5, 6-7, 8-9, 10+ for anxiety, and 0-7, 8-9, 10-12, 13-16, 17+ for stress subscales respectively. The addition of the three subscales into a total DASS-21 score gives an indication of general distress. This measure has good reliability and validity (Henry & Crawford, 2005; Lovibond & Lovibond, 1995a, 1995b; Sinclair et al., 2012).

Eating disorder related experiences

The main ‘initial’ VAS were completed at baseline (2)/TP1 to assess the salience of the FCT from TP1 to TP2. These scales included an assessment of ‘levels of stress’, ‘urge to restrict’, ‘urge to exercise’, ‘levels of anxiety’, ‘feeling full’ and ‘feeling fat’ (Appendix G.1). Following the first FCT these VAS were administered throughout the RCT (i.e. from TP2 – TP5) and used within primary and secondary outcomes.

Outcome measures

Primary outcome

The primary outcome variable was a composite ‘core AN symptoms’ computed by the summation of VAS scores on urge to restrict (0-10), levels of feeling full (0-10) and fat (0-10) with a total possible score of 30. The urge to exercise VAS was not included in this composite outcome as it was deemed as a highly

heterogeneous symptom of AN, which varies between individuals and sub-types of AN (i.e. excessive exercise is present in some people with AN, but not others). To assess the effects of rTMS on the primary outcome, VAS were collected at TP2 (pre rTMS), TP3 (immediately after rTMS), TP4 (the end/20 minutes following the rTMS session) and TP5 (24 hours following).

Secondary outcomes

Secondary outcomes included a composite 'anxiety and stress' outcome, computed by summation of the stress (0-10) and anxiety (0-10) VAS, with a total possible score of 20. The six individual 10cm VAS were also analysed separately, along with the additional VAS that were included in the FCT relating to calmness/tension, mood, hunger, urge to eat, urge to binge eat and urge to be sick or purge (Appendix G.2). The secondary composite anxiety and stress outcome, and the six individual VAS were collected at TP2 (pre rTMS), TP3 (immediately after rTMS), TP4 (the end/20 minutes following the rTMS session) and TP5 (24 hours following). At TP5 the VAS information was collected over the phone, therefore participants had to respond by giving a number between 1 and 10. The additional VAS were administered during the two FCT (i.e. pre and post rTMS), therefore were only completed twice (at TP2 and TP3).

'Blinding' success

At the end of the 24 hour follow-up phone call participants were asked to guess which stimulation type (real/sham) they thought they had received and then asked to indicate how sure they were of this decision by giving a number between 0 (completely unsure) and 10 (completely sure).

Similarly, after the session, researchers were asked to guess which stimulation type (real/sham) they thought the participant had received and then asked to indicate on a VAS how sure they were of their decision (0 = completely unsure and 10 = completely sure). The choice of real/sham rTMS for researchers was not titrated according to their previous choices or against upcoming allocations. This meant that they could feasibly guess all real or all sham, i.e. they could guess a stimulation type more regularly than what was actually delivered.

Statistical analyses

Statistical analyses were performed using IBM® SPSS® software (Version 22). Following consultation with a statistician, when normality or the ANOVA homogeneity of variance assumption was violated (assessed via Kolmogorov-Smirnov and Levene's test statistics respectively) log transformations or other non-parametric alternatives were used and post-hoc bootstrapping methods with Bonferroni corrections were employed. Where Mauchly's test of sphericity was violated Greenhouse-Geisser corrections are reported. All tests were two-tailed and the level of significance was set at $\alpha = 0.05$.

Baseline(2) data regarding demographic information and psychopathology were normally distributed. Therefore, independent t-tests and Pearson's chi-squared tests (χ^2) were used to compare characteristics of the real/sham groups. Also, paired t-tests were used to assess the salience of the FCT.

Data regarding the primary and secondary outcomes were normally distributed. Therefore, the effects of real versus sham rTMS were evaluated using a mixed ANOVA (group: real/sham rTMS x time: TP3, TP4 and TP5) controlling for scores at TP2 (this was used as baseline scores as it was immediately prior to the real/sham rTMS intervention). The effects of real versus sham rTMS on the additional FCT VAS were evaluated using a mixed ANOVA (group: real/sham rTMS x time: TP2, TP3).

Pearson's chi-square (χ^2) was used to assess whether or not participants and researchers correctly guessed experimental condition (real/sham rTMS) better than chance (i.e. 50%). Also, χ^2 was used to compare the ability of participants within real/sham groups, and the ability of researchers, to correctly guess stimulation type. Additionally, t-tests were used to compare levels of certainty in both participants and researchers on how sure they were of their decision regarding which intervention they received.

Partial eta squared (η^2) and Cohen's *d* effect sizes are reported for mixed ANOVAs and t-tests respectively. Partial eta squared is automatically computed within SPSS by dividing the sums of squares for the effect of interest by the total

sums of squares i.e. $\eta^2 = SS_{\text{between}}/SS_{\text{total}}$ (Levine & Hullett, 2002). Cohen's d was computed by dividing the difference in means by the pooled standard deviation i.e. $d = M_1 - M_2/\sqrt{(SD_1^2 + SD_2^2)/2}$. Interpretation of the magnitude of η^2 is 0.01-0.06 = small; 0.06-0.14 = medium and > 0.14 = large; and for Cohen's d effect sizes 0.15-0.40 = small; 0.4-0.75 = medium and > 0.75 : large (Cohen, 1988).

Results

Two participants randomised to real rTMS withdrew following the first few trains of rTMS (due to discomfort) and were excluded from statistical analyses. Therefore, 49 female (by chance), right-handed individuals, randomised to real ($n = 21$, restrictive = 13, binge/purge = 8) and sham ($n = 28$, restrictive = 15, binge/purge = 13) were included in the analyses.

Baseline characteristics

Table 3.2 presents demographic characteristics, ED and psychiatric history and psychopathology scores for the entire sample and for each of the real/sham rTMS groups. There were no significant group differences between real/sham groups on demographic information at baseline (2). In regards to psychopathology, groups differed on the EDE-Q weight [$t(47) = -2.05$, $p = 0.046$, $d = 0.60$] and shape concern [$t(47) = -2.06$, $p = 0.045$, $d = 0.60$] subscales, where the sham group demonstrated significantly greater ED psychopathology. Both groups had moderate/severe levels of depression, anxiety and stress.

Given the uneven proportion of subtypes between real/sham groups (real: 62% restrictive, 38% binge/purge; sham: 54% restrictive, 46% binge/purge) and the differences in ED psychopathology reported between the groups, we compared psychopathology between AN subtypes. Those with a binge/purge diagnosis scored significantly higher across the EDE-Q global scale [$t(47) = -2.06$, $p = 0.045$, $d = 0.60$] (restrictive: $M = 3.91$, $SD = 1.24$; binge/purge: $M = 4.59$, $SD = 0.98$), restraint [$t(46.76) = -2.36$, $p = 0.022$, $d = 0.69$] (restrictive: $M = 3.93$, $SD = 1.56$; binge/purge: $M = 4.82$, $SD = 1.08$) and eating concern subscales [$t(47) = -2.24$, $p = 0.030$, $d = 0.65$] (restrictive: $M = 3.51$, $SD = 1.30$; binge/purge: $M = 4.29$,

$SD = 1.07$) and the DASS-21 depression sub-scale [$t(47) = -2.54, p = 0.014, d = 0.74$] (restrictive: $M = 9.43, SD = 5.54$; binge/purge: $M = 13.57, SD = 5.77$).

Table 3.2 Baseline characteristics; demographic information, psychiatric history and current psychopathology. Mean \pm SD reported

	Entire sample (<i>N</i> = 49)	Real rTMS (<i>n</i> = 21)	Sham rTMS (<i>n</i> = 28)
Demographic information			
Age	26.65 \pm 8.73	25.29 \pm 6.88	27.68 \pm 9.89
Weight	44.57 \pm 5.83	45.57 \pm 6.11	43.86 \pm 5.62
Ethnicity	White (<i>n</i> = 44) Asian (<i>n</i> = 1) Other (<i>n</i> = 4)	White (<i>n</i> = 19) - Other (<i>n</i> = 2)	White (<i>n</i> = 25) Asian (<i>n</i> = 1) Other (<i>n</i> = 2)
Marital status	Single (<i>n</i> = 45) Married (<i>n</i> = 4)	Single (<i>n</i> = 20) Married (<i>n</i> = 1)	Single (<i>n</i> = 25) Married (<i>n</i> = 3)
Non-smokers: smokers	34:15	15:6	19:9
Highest level of education obtained	GCSE (<i>n</i> = 2) AS levels (<i>n</i> = 1) A levels (<i>n</i> = 24) Degree (<i>n</i> = 20) Masters (<i>n</i> = 2)	GCSE (<i>n</i> = 1) - A levels (<i>n</i> = 7) Degree (<i>n</i> = 11) Masters (<i>n</i> = 2)	GCSE (<i>n</i> = 1) AS levels (<i>n</i> = 1) A levels (<i>n</i> = 17) Degree (<i>n</i> = 9) -
Alcohol consumption Days/week & Units/day	2.59 \pm 2.17 4.10 \pm 3.42	2.55 \pm 2.43 2.90 \pm 2.85	2.04 \pm 1.60 3.80 \pm 3.01
Eating disorder history			
Anorexia sub- type	R (<i>n</i> = 28) B/P (<i>n</i> = 21)	R (<i>n</i> = 13) B/P (<i>n</i> = 8)	R (<i>n</i> = 15) B/P (<i>n</i> = 13)
BMI	16.52 \pm 1.68	16.73 \pm 1.59	16.38 \pm 1.76
Lowest previous BMI since onset	13.34 \pm 1.73	13.76 \pm 1.28	13.04 \pm 1.95
Illness duration	10.32 \pm 7.61	9.05 \pm 7.02	11.27 \pm 8.01
Number of meals per day	2.18 \pm 0.95	2.05 \pm 0.93	2.29 \pm 0.97

Table 3.2 (continued). Baseline characteristics; demographic information, psychiatric history and current psychopathology. Mean \pm SD reported.

	Entire sample (<i>N</i> = 49)	Real rTMS (<i>n</i> = 21)	Sham rTMS (<i>n</i> = 28)
Psychiatric history			
Currently receiving psychological treatment	Yes (<i>n</i> = 36) No (<i>n</i> = 13)	Yes (<i>n</i> = 13) No (<i>n</i> = 8)	Yes (<i>n</i> = 23) No (<i>n</i> = 5)
Diagnosed co-morbidities	Depression(<i>n</i> = 22) Anxiety (<i>n</i> = 1) OCD (<i>n</i> = 4)	Depression (<i>n</i> = 8) - -	Depression(<i>n</i> = 14) Anxiety (<i>n</i> = 1) OCD (<i>n</i> = 4)
Number on medications	34/49 (69%) Fluoxetine (<i>n</i> = 20) Venlafaxine (<i>n</i> = 2) Citalopram (<i>n</i> = 3) Olanzapine (<i>n</i> = 1) Mirtazapine (<i>n</i> = 3) Diazepam (<i>n</i> = 2) Sertraline (<i>n</i> = 3) > 2 meds (<i>n</i> = 5)	12/21 (57%) Fluoxetine (<i>n</i> = 8) Venlafaxine (<i>n</i> = 1) Citalopram (<i>n</i> = 1) Olanzapine (<i>n</i> = 1) - Diazepam (<i>n</i> = 2) Sertraline (<i>n</i> = 1) > 2 meds (<i>n</i> = 2)	22/28 (79%) Fluoxetine (<i>n</i> = 12) Venlafaxine (<i>n</i> = 1) Citalopram (<i>n</i> = 2) - Mirtazapine (<i>n</i> = 3) - Sertraline (<i>n</i> = 2) > 2 meds (<i>n</i> = 3)
Eating disorder examination questionnaire (EDE-Q)			
Global score	4.20 \pm 1.17	3.90 \pm 1.26	4.43 \pm 1.07
Restraint	4.31 \pm 1.43	4.17 \pm 1.68	4.41 \pm 1.23
Eating concern	3.85 \pm 1.26	3.63 \pm 1.16	4.01 \pm 1.32
Weight concern	3.97 \pm 1.50	3.48 \pm 1.66	4.33 \pm 1.28
Shape concern	4.69 \pm 1.13	4.31 \pm 1.22	4.96 \pm 0.98
Depression, anxiety and stress scale (DASS-21)			
Total score	32.10 \pm 12.94	29.67 \pm 13.65	33.93 \pm 12.31
Depression	11.20 \pm 5.95	10.14 \pm 5.98	12.00 \pm 5.92
Anxiety	7.88 \pm 4.36	7.05 \pm 4.29	8.50 \pm 4.37
Stress	13.02 \pm 4.61	12.48 \pm 5.00	13.43 \pm 4.36

Salience of the food challenge task

Table 3.3 shows the descriptive statistics for the entire sample and for the real/sham groups separately of the composite outcomes and individual VAS scores before and after the first delivery of the FCT. By chance, at the beginning of the testing session, i.e. baseline(2)/TP1, the sham group scored significantly higher on core AN symptoms [$t(31.97) = -2.22, p = 0.034, d = 0.78$] and levels of feeling fat [$t(36.21) = -2.62, p = 0.013, d = 0.87$] than the real group, however these differences were not significant following the FCTpre (TP2). There were no differences between AN subtypes across measures at baseline(2)/TP1.

The salience of the FCT (TP1 to TP2) was assessed for the entire sample and separately within each of the real/sham rTMS groups. As a whole, the FCT significantly increased scores on the composite anxiety and stress outcome [$t(48) = -2.08, p = 0.043, d = 0.60$] and the individual VAS regarding levels of anxiety [$t(48) = -2.19, p = 0.034, d = 0.63$]. There was also a trend indicating that the FCT increased participants' urge to restrict [$t(48) = -1.70, p = 0.095, d = 0.49$].

When assessing the effects of the FCT separately for each group, the FCT did not significantly increase scores on the primary core AN symptom outcome, the secondary composite anxiety and stress outcome, or individual VAS in either group. However, there was a trend for an increase in scores on the composite anxiety and stress outcome in the sham group [$t(27) = -1.85, p = 0.075, d = 0.34$], and across the individual VAS regarding levels of anxiety [$t(20) = -1.87, p = 0.076, d = 0.20$] and levels of stress [$t(27) = -1.76, p = 0.090, d = 0.29$] in the real and sham group respectively.

Table 3.3 Composite outcomes and individual VAS before and after the first FCT. Mean \pm SD reported.

	Entire sample (<i>N</i> = 49)		Real rTMS (<i>n</i> = 21)		Sham rTMS (<i>n</i> = 28)	
	TP1	TP2	TP1	TP2	TP1	TP2
Composite outcomes						
Core AN symptoms	18.75 \pm 6.05	19.40 \pm 6.59	16.49 \pm 7.11	17.63 \pm 7.35	20.43 \pm 4.56	20.72 \pm 5.75
Anxiety & Stress	10.45 \pm 5.82	11.74 \pm 5.87	9.90 \pm 6.54	10.48 \pm 6.28	10.86 \pm 5.31	12.69 \pm 5.47
Individual visual analogue scales						
Levels of stress	5.03 \pm 3.04	5.45 \pm 2.99	4.72 \pm 3.23	4.61 \pm 3.21	5.27 \pm 2.90	6.08 \pm 2.70
Urge to restrict	6.63 \pm 2.73	7.24 \pm 2.62	6.24 \pm 3.06	7.05 \pm 2.19	6.92 \pm 2.47	7.38 \pm 2.94
Levels of anxiety	5.42 \pm 3.12	6.29 \pm 3.14	5.18 \pm 3.61	5.87 \pm 3.32	5.60 \pm 2.75	6.61 \pm 3.02
Urge to exercise	4.74 \pm 3.50	4.23 \pm 3.40	3.71 \pm 3.57	2.99 \pm 3.27	5.50 \pm 3.30	5.16 \pm 3.24
Levels of feeling full	5.59 \pm 2.97	5.63 \pm 3.39	4.89 \pm 2.89	5.03 \pm 3.39	6.11 \pm 2.97	6.08 \pm 3.38
Levels of feeling fat	6.53 \pm 2.75	6.53 \pm 2.99	5.37 \pm 2.96	5.55 \pm 3.23	7.40 \pm 2.26	7.27 \pm 2.61

The individual outcomes were measured on 10cm visual analogue scales (VAS) and scores ranged between 0 (not stressed/no urge to restrict/not anxious/no urge to exercise/not feeling full or fat at all) to 10 (extremely stressed/strong urge to restrict/anxious/strong urge to exercise/feeling extremely full or fat). The composite 'core AN symptom' outcome was computed by adding scores on the three VAS urge to restrict, levels of feeling full and levels of feeling fat, therefore 'core AN symptom' scores could range from 0 to 30. The composite 'anxiety & stress' outcome was computed by adding scores on the two anxiety and stress VAS and could therefore range from 0 to 20.

Primary outcome

Mixed ANOVA analyses controlling for pre-rTMS (TP2) scores showed no significant interaction between stimulation type and time. There was however, an effect of time and a trend toward group differences (Table 3.4); those who had real rTMS reported reduced AN symptoms. Post hoc, bootstrapped comparisons suggested these group differences were significant at each of the three time points; TP3 [$t(47) = -2.31, p = 0.030, d = 0.67$], TP4 [$t(47) = -2.24, p = 0.035, d = 0.65$] and TP5 [$t(47) = -2.51, p = 0.021, d = 0.73$]. However, these differences were no longer significant following Bonferroni corrections for multiple comparisons ($p = 0.017$).

Secondary outcomes

Mixed ANOVA analyses, controlling for pre-rTMS (TP2) scores, regarding the composite anxiety and stress outcome, showed no significant interaction or group differences. There was, however, an effect of time (Table 3.4).

Across the individual VAS, mixed ANOVA analyses controlling for pre-rTMS (TP2) scores demonstrated no interaction effects (Table 3.5). There was an effect of time on levels of stress, anxiety, levels of feeling full and levels of feeling fat. There was also a trend for between group differences on levels of feeling fat; those who had real rTMS reported reduced levels of feeling fat. Post hoc, bootstrapped comparisons suggested that these group differences were significant at each of the three time points; TP3 [$t(47) = -2.50, p = 0.030, d = 0.73$], TP4 [$t(47) = -2.82, p = 0.015, d = 0.82$] and TP5 [$t(47) = -2.27, p = 0.036, d = 0.66$]. However, following Bonferroni corrections for multiple comparisons ($p = 0.017$) only differences at TP4 (end of the testing session) remained significant. There were no significant interaction effects across any of the additional VAS administered during the FCT (Table 3.6). There was a significant effect of time and a trend for group differences on reported levels of calmness/tension, in addition to an effect of time (but no group differences) on reported mood, hunger, urge to eat, and urge to be sick or purge. There was no effect of time or group on participants urge to binge eat.

Table 3.4 Mixed ANOVA results of the composite outcomes following real/sham rTMS. Mean \pm SD reported.

	Time point	Real rTMS (<i>n</i> = 21)	Sham rTMS (<i>n</i> = 28)	ANOVA Time	ANOVA Group	ANOVA Interaction Group x Time
Core AN Symptoms	Post rTMS & FCTpost (TP3)	13.70 \pm 7.29	17.75 \pm 5.01	<i>F</i> (1.35) = 13.58 <i>p</i> < 0.001 η^2 = 0.23	<i>F</i> (1) = 3.86 <i>p</i> = 0.056 η^2 = 0.08	<i>F</i> (1.35) = 0.14 <i>p</i> = 0.780 η^2 = 0.00
	End of session (TP4)	12.58 \pm 7.44	16.73 \pm 5.49			
	24 hours follow-up (TP5)	15.90 \pm 5.17	19.64 \pm 5.14			
Anxiety & Stress	Post rTMS & FCTpost (TP3)	8.12 \pm 6.23	9.52 \pm 5.79	<i>F</i> (1.60) = 8.26 <i>p</i> = 0.001 η^2 = 0.15	<i>F</i> (1) = 0.01 <i>p</i> = 0.929 η^2 = 0.00	<i>F</i> (1.60) = 0.77 <i>p</i> = 0.441 η^2 = 0.02
	End of session (TP4)	7.25 \pm 6.51	8.88 \pm 5.72			
	24 hours follow-up (TP5)	8.62 \pm 4.32	10.68 \pm 4.72			

The composite 'core AN symptom' outcome was computed by adding scores across the three 10cm visual analogue scales (VAS) relating to the urge to restrict, levels of feeling full and levels of feeling fat and therefore scores could range from 0 to 30. The composite 'anxiety & stress' outcome was computed by adding scores across the two 10cm anxiety and stress VAS and could therefore range from 0 to 20.

Table 3.5 Mixed ANOVA results of the ‘initial’ VAS following real/sham rTMS. Mean \pm SD reported.

	Time point	Real rTMS (<i>n</i> = 21)	Sham rTMS (<i>n</i> = 28)	ANOVA Time	ANOVA Group	ANOVA Interaction Group x Time
Levels of stress	Post rTMS & FCTpost (TP3)	3.87 \pm 3.15	4.52 \pm 2.87	<i>F</i> (1.55) = 8.40 <i>p</i> = 0.001 η^2 = 0.15	<i>F</i> (1) = 0.34 <i>p</i> = 0.565 η^2 = 0.01	<i>F</i> (1.55) = 0.95 <i>p</i> = 0.370 η^2 = 0.02
	End of session (TP4)	3.65 \pm 3.26	4.43 \pm 2.90			
	24 hours follow-up (TP5)	4.24 \pm 2.28	5.21 \pm 2.38			
Urge to restrict	Post rTMS & FCTpost (TP3)	5.62 \pm 3.01	6.17 \pm 2.39	<i>F</i> (1.49) = 2.21 <i>p</i> = 0.130 η^2 = 0.05	<i>F</i> (1) = 1.26 <i>p</i> = 0.268 η^2 = 0.03	<i>F</i> (1.49) = 0.88 <i>p</i> = 0.393 η^2 = 0.02
	End of session (TP4)	5.18 \pm 3.04	5.76 \pm 2.52			
	24 hours follow-up (TP5)	5.57 \pm 2.48	6.79 \pm 2.11			
Levels of anxiety	Post rTMS & FCTpost (TP3)	4.25 \pm 3.18	5.00 \pm 3.10	<i>F</i> (1.72) = 4.93 <i>p</i> = 0.013 η^2 = 0.10	<i>F</i> (1) = 0.74 <i>p</i> = 0.395 η^2 = 0.02	<i>F</i> (1.72) = 0.37 <i>p</i> = 0.657 η^2 = 0.01
	End of session (TP4)	3.60 \pm 3.27	4.45 \pm 2.94			
	24 hours follow-up (TP5)	4.38 \pm 2.33	5.46 \pm 2.63			

These were measured on 10cm visual analogue scales (VAS); scores could range from 0 (not stressed/no urge to restrict/not anxious at all) to 10 (extremely stressed/strong urge to restrict/anxious).

Table 3.5 (continued) Mixed ANOVA results of the ‘initial’ VAS following real/sham rTMS. Mean \pm SD reported.

	Time Point	Real rTMS (<i>n</i> = 21)	Sham rTMS (<i>n</i> = 28)	ANOVA Time	ANOVA Group	ANOVA Interaction Group x Time
Urge to exercise	Post rTMS & FCTpost (TP3)	2.51 \pm 3.26	4.47 \pm 3.22	<i>F</i> (1.35) = 9.50 <i>p</i> = 0.001 η^2 = 0.17	<i>F</i> (1) = 0.33 <i>p</i> = 0.566 η^2 = 0.01	<i>F</i> (1.35) = 0.96 <i>p</i> = 0.358 η^2 = 0.20
	End of session (TP4)	2.59 \pm 3.40	4.28 \pm 3.30			
	24 hours follow-up (TP5)	3.57 \pm 2.87	4.36 \pm 2.70			
Levels of feeling full	Post rTMS & FCTpost (TP3)	3.53 \pm 2.80	4.91 \pm 3.18	<i>F</i> (1.23) = 21.89 <i>p</i> < 0.001 η^2 = 0.32	<i>F</i> (1) = 1.24 <i>p</i> = 0.272 η^2 = 0.03	<i>F</i> (1.23) = 0.07 <i>p</i> = 0.851 η^2 = 0.00
	End of session (TP4)	3.33 \pm 2.73	4.44 \pm 3.22			
	24 hours follow-up (TP5)	5.14 \pm 2.90	6.00 \pm 2.70			
Levels of feeling fat	Post rTMS & FCTpost (TP3)	4.55 \pm 3.19	6.68 \pm 2.76	<i>F</i> (1.44) = 11.40 <i>p</i> < 0.001 η^2 = 0.20	<i>F</i> (1) = 3.01 <i>p</i> = 0.089 η^2 = 0.06	<i>F</i> (1.44) = 0.43 <i>p</i> = 0.587 η^2 = 0.01
	End of session (TP4)	4.07 \pm 3.41	6.52 \pm 2.68			
	24 hours follow-up (TP5)	5.19 \pm 2.56	6.86 \pm 2.53			

These were measured on 10cm visual analogue scales (VAS); scores could range from 0 (no urge to exercise/not feeling full or fat at all) to 10 (extremely strong urge to exercise/feeling extremely full or fat).

Table 3.6 Mixed ANOVA results of the ‘additional’ VAS following real/sham rTMS. Mean \pm SD reported.

	Time Point	Real rTMS (<i>n</i> = 21)	Sham rTMS (<i>n</i> = 28)	ANOVA Time	ANOVA Group	ANOVA Interaction Group x Time
Calmness	Post FCTpre/pre rTMS (TP2)	5.61 \pm 3.16	6.79 \pm 2.14	<i>F</i> (1) = 26.75 <i>p</i> < 0.001 η^2 = 0.36	<i>F</i> (1) = 2.91 <i>p</i> = 0.095 η^2 = 0.06	<i>F</i> (1) = 0.00 <i>p</i> = 0.982 η^2 = 0.00
	Post rTMS & FCTpost (TP3)	4.01 \pm 2.93	5.21 \pm 2.42			
Mood	Post FCTpre/pre rTMS (TP2)	4.12 \pm 1.88	3.79 \pm 1.58	<i>F</i> (1) = 13.32 <i>p</i> = 0.001 η^2 = 0.22	<i>F</i> (1) = 0.46 <i>p</i> = 0.499 η^2 = 0.01	<i>F</i> (1) = 0.00 <i>p</i> = 0.972 η^2 = 0.00
	Post rTMS & FCTpost (TP3)	4.88 \pm 2.13	4.56 \pm 1.68			
Hunger	Post FCTpre/pre rTMS (TP2)	2.88 \pm 2.68	3.42 \pm 3.54	<i>F</i> (1) = 15.29 <i>p</i> < 0.001 η^2 = 0.25	<i>F</i> (1) = 0.57 <i>p</i> = 0.455 η^2 = 0.01	<i>F</i> (1) = 0.07 <i>p</i> = 0.793 η^2 = 0.00
	Post rTMS & FCTpost (TP3)	4.27 \pm 3.06	5.02 \pm 3.07			

These were measured on 10cm visual analogue scales (VAS); scores could range from 0 (extremely calm/extremely low/not hungry at all) to 10 (extremely tense/extremely high/extremely hungry).

Table 3.6 (continued) Mixed ANOVA results of the ‘additional’ VAS following real/sham rTMS. Mean \pm SD reported.

	Time Point	Real rTMS (<i>n</i> = 21)	Sham rTMS (<i>n</i> = 28)	ANOVA Time	ANOVA Group	ANOVA Interaction Group x Time
Urge to eat	Post FCTpre/pre rTMS (TP2)	2.38 \pm 2.60	2.97 \pm 3.37	<i>F</i> (1) = 13.11 <i>p</i> < 0.001 η^2 = 0.22	<i>F</i> (1) = 0.51 <i>p</i> = 0.478 η^2 = 0.01	<i>F</i> (1) = 0.01 <i>p</i> = 0.917 η^2 = 0.00
	Post rTMS & FCTpost (TP3)	3.93 \pm 2.84	4.43 \pm 3.10			
Urge to binge eat	Post FCTpre/pre rTMS (TP2)	0.99 \pm 1.95	2.22 \pm 3.24	<i>F</i> (1) = 0.05 <i>p</i> = 0.827 η^2 = 0.00	<i>F</i> (1) = 2.36 <i>p</i> = 0.131 η^2 = 0.05	<i>F</i> (1) = 0.31 <i>p</i> = 0.579 η^2 = 0.01
	Post rTMS & FCTpost (TP3)	1.12 \pm 2.13	1.91 \pm 2.83			
Urge to be sick/ purge	Post FCTpre/pre rTMS (TP2)	2.27 \pm 3.14	3.26 \pm 3.68	<i>F</i> (1) = 7.65 <i>p</i> = 0.008 η^2 = 0.14	<i>F</i> (1) = 2.19 <i>p</i> = 0.145 η^2 = 0.04	<i>F</i> (1) = 0.58 <i>p</i> = 0.450 η^2 = 0.01
	Post rTMS & FCTpost (TP3)	1.10 \pm 2.03	2.60 \pm 3.20			

These were measured on 10cm visual analogue scales (VAS); scores could range from 0 (no urge to eat/binge eat/be sick or purge) to 10 (extremely strong urge to eat/binge eat/be sick or purge).

Blinding success

Participants guessed stimulation type better than chance [$\chi^2(1) = 4.59, p = 0.032, N = 49$] as only 35% of participants incorrectly guessed stimulation type. However, there were no significant differences between real/sham groups in their ability to correctly guess stimulation type [$\chi^2(1) = 1.08, p = 0.299, N = 49$]; 43% who had real rTMS thought they had sham, while 29% who had sham rTMS thought they received real (see Figure 3.4). Both groups had similar rates of certainty regarding how sure they were of which rTMS they had [$t(47) = -0.03, p = 0.975, d = 0.01$]; real ($M = 4.67, SD = 2.32$), sham ($M = 4.79, SD = 2.78$).

In contrast, researchers were not able to guess stimulation type better than chance [$\chi^2(1) = 0.51, p = 0.475, N = 49$] as researchers incorrectly guessed in 45% of cases. However, between real/sham groups there were significant differences in the ability of researchers to correctly guess stimulation type [$\chi^2(1) = 9.93, p = 0.002, N = 49$]; researchers were incorrect 19% of the time for those who had real and 64% for those who had sham (see Figure 3.5). Rates of certainty in researchers were similar across groups [$t(47) = -0.29, p = 0.776, d = 0.08$]; real ($M = 2.24, SD = 2.32$), sham ($M = 2.43, SD = 2.30$). Compared to participants, researchers were less sure about their guess of rTMS allocation [$t(48) = -5.06, p < 0.001, d = 1.46$]; researchers ($M = 2.35, SD = 2.29$), participants ($M = 4.78, SD = 2.57$).

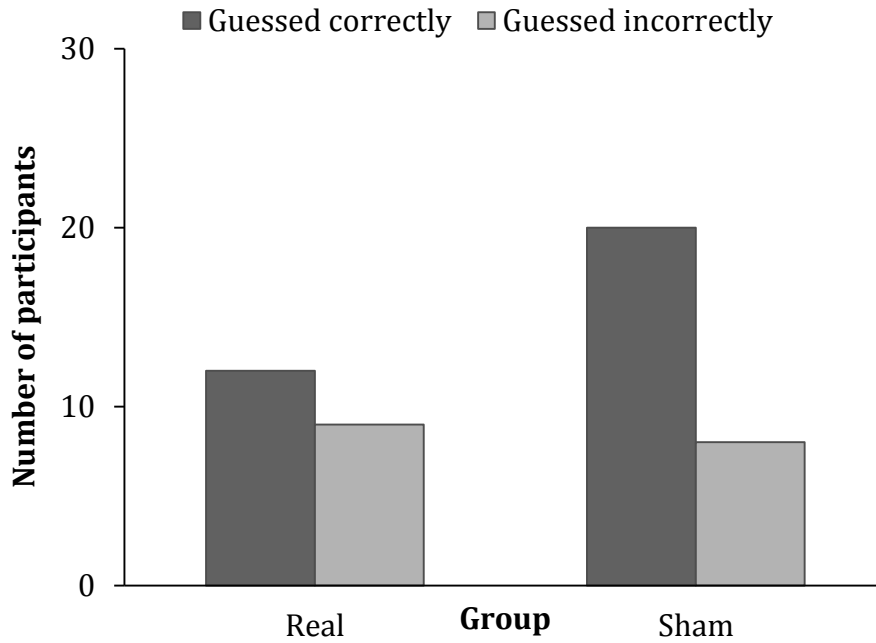


Figure 3.4 Number of participants who correctly or incorrectly guessed stimulation type

In the real group 12 participants guessed correctly and 9 guessed incorrectly. In the sham group, 20 participants guessed correctly and 8 guessed incorrectly.



Figure 3.5 The frequency of researchers correctly or incorrectly guessing stimulation type allocated to participants

Researchers correctly guessed allocation on 17 and 10 occasions (therefore incorrectly guessing 4 and 18 times) in the real and sham groups respectively.

Discussion

The results of this RCT of rTMS in AN support our primary hypothesis; individuals who received real rTMS (compared to sham) reported reduced AN symptoms. However, there were no significant interaction effects as core AN symptoms were also reduced following sham rTMS. Therefore, there is some indication of an rTMS placebo effect.

In relation to our secondary outcomes, levels of feeling fat showed a similar trend, in that those who received real rTMS reported reduced levels of feeling fat. Compared to sham, real rTMS did not significantly reduce levels of stress and anxiety, or individual scores across ED related experiences, such as the urge to restrict or exercise. Moreover, there were no interaction or group effects on other symptoms assessed during the food cue-exposure task (e.g. mood, hunger, urge to eat etc.). Whilst broad improvements over time across secondary outcomes were reported in both real/sham groups, there were no between group differences. Finally, participants (but not researchers) correctly guessed stimulation type more so than chance. However, in participants, there were no group differences in the ability to correctly guess stimulation type. Therefore, blinding was partially successful.

Our data are in partial agreement with the existing literature. Our pilot study found that a single session of rTMS reduced anxiety, levels of feeling full and feeling fat (Van den Eynde, Guillaume, et al., 2013) and our 20 rTMS session case studies also demonstrate within-session reductions across these measures (see Chapter 5 or McClelland, Bozhilova, Nestler, et al., 2013). However, these studies lack a control condition and whilst our current data replicate short-term reductions in AN symptoms following rTMS, generally this was not significantly more so than sham. Combining the individual measures of AN symptoms into the composite, primary core AN symptom outcome differentiated real and sham rTMS groups and this suggests that the current study is underpowered. Importantly, our findings of reduced AN symptoms following real rTMS were not accompanied by similar improvements in mood. This is in agreement with existing literature that shows no improvements in mood following a single

session of rTMS (Baeken et al., 2009; Baeken et al., 2014) and indicates that the improvements in AN symptoms following rTMS reported here are independent of effects on comorbid symptoms.

With regards to blinding success, our results are similar to those previously reported in BN (Van den Eynde et al., 2010). However, participants guessed stimulation type better than chance and researchers were significantly more able to guess allocation to real rather than sham rTMS. This is likely to be a result of not titrating choices for researchers based on previous/upcoming guesses and their chance inclination to choose real rTMS more often than it was actually delivered. Also, researchers were less sure about their choice of rTMS allocation. Given that the researchers who carried out pre/post rTMS experimental tasks were not in the room when people had rTMS, this indicates that the rTMS procedure itself impacts the certainty regarding decision making as to which intervention was delivered.

Study sample

The sample of AN in the current research had particularly severe and enduring forms of AN, indicated by their long illness duration, lowest reported BMI since illness onset and ED psychopathology. This is likely to have impeded the effects of just a single-session of rTMS; arguably less severe symptoms in participants who have not had AN for as long may be more susceptible to brief rTMS exposure.

By chance, baseline ED and general psychopathology scores across all primary and secondary outcome scores were consistently, and at times significantly, higher within the sham group. This is likely to be due to uneven proportions of subtypes between groups; the sham group had more individuals with a binge/purge AN subtype, who demonstrated higher symptomatology than those with a restrictive subtype. Whilst the differences between real/sham groups at baseline became non-significant following the first food exposure task, these initial group differences are likely to have confounded group effects and must be considered in the interpretation of results. It is possible that the reduced AN

symptoms and levels of feeling fat following real rTMS reflect a natural progression towards the group differences that existed initially.

Moreover, in the current sample the food exposure task was not as salient as reported in our previous AN rTMS pilot study (Van den Eynde, Guillaume, et al., 2013). Whilst significance was reached when looking at the effects of the task on the entire sample as a whole, these did not remain significant when the real/sham groups were considered separately. This further suggests that this study is somewhat underpowered. Additionally, given literature suggesting the importance of state-related neural activity on the effects of rTMS (Gersner et al., 2011) and the concurrent use of exposure techniques with rTMS (Baek et al., 2012), the fact that our food exposure task was not as salient as we had hoped, i.e. it did not significantly increase ED related experiences, may have diminished rTMS effects on AN symptoms in this group.

Whilst a higher proportion of individuals in the sham group were on medication, over half of the participants in both groups were medicated. Increases in facilitatory plasticity have been reported following selective serotonin reuptake inhibitor (SSRI) intake (Normann, Schmitz, Furmaier, Doing, & Bach, 2007) and similarly, citalopram has been shown to enhance the facilitatory plasticity reported to be induced by tDCS (Nitsche, Kuo, et al., 2009). Therefore, it is possible that the patients who were on such medications had an enhanced response to rTMS, which may have confounded results.

An additional complication of studying AN (which was relevant in this sample) is symptom heterogeneity between and within AN subtypes. The symptoms that characterise AN sub-types are often argued to have different underlying neural mechanisms (Brooks et al., 2012). Therefore, they may need to be studied with separate and tailored neuromodulation protocols in order to elicit symptom-specific improvements. Whilst the current study aimed to overcome this by stratified randomisation procedures, larger numbers are needed in order make further comparisons of rTMS effects on particular ED symptoms and between AN subtypes.

Physiological mechanisms

A number of potential mechanistic hypotheses may explain the effects of rTMS in AN reported here. Short-term improvements in ED symptoms may be due to direct, focal modulation of the DLPFC and dorsal neural circuitry responsible for regulation of emotion, appetite and cognitive control. Alternatively, recent evidence suggests that rTMS applied to the PFC induces effects on remote, subcortical areas (George et al., 1999) and therefore, neural modulation of the DLPFC with rTMS in AN may remotely effect mesolimbic responses to food and other ED salient stimuli.

Also, rTMS induced changes in neural circuitry may occur in a number of ways. Changes to neuroplasticity markers have been reported following rTMS (Esslinger et al., 2014; Gersner et al., 2011; Medina & Tunez, 2013; Ridding & Rothwell, 2007; Vlachos et al., 2012) and may underlie the effects reported here. Specifically, BDNF is a proposed biomarker of response to rTMS (Fidalgo et al., 2014) and is increased following HF rTMS (Gersner et al., 2011; Zanardini et al., 2006). Given that alterations in BDNF levels have been reported across different stages of AN, rTMS may induce neuroplasticity via the modulation of BDNF expression (Brandys, Kas, van Elburg, Campbell, & Adan, 2011; Zwipp et al., 2014). Additionally, modulation of dopamine (Cho & Strafella, 2009) and serotonin concentrations (Baeken et al., 2011; Kanno, Matsumoto, Togashi, Yoshioka, & Mano, 2003) has been reported following HF rTMS to the PFC. As alterations in these neurotransmitters have been reported in AN (Bailer et al., 2013; Frank et al., 2005; Frank et al., 2002) rTMS may exert therapeutic effects in AN via modulation of their expression.

Strengths

This study is the first neuromodulation protocol in AN with an active control condition (Khedr, Elfetoh, et al., 2014; McClelland, Bozhilova, Nestler, et al., 2013; Van den Eynde, Guillaume, et al., 2013). The MEP method of estimating MT is more accurate, conservative and safer than other methods. However, while it is recommended (Rossi et al., 2009), it typically results in lower estimates of MT and, as rTMS intensity is based on MT, this may have resulted in

weaker rTMS protocols than used previously. Finally, neuronavigation provides a more individualised, accurate and effective method of targeting the left DLPFC than the previously employed 5cm anterior method (Fitzgerald et al., 2009; Herwig, Padberg, et al., 2001; Rossi et al., 2009).

Limitations

The main limitation of this study is its lack of power. It was short of the required sample size and therefore, we may have had more significant effects of rTMS on both primary and secondary outcomes and also would have been better positioned to control for additional covariates if participant numbers were larger. Additionally, whilst the use of VAS has demonstrated utility in clinical research (McCormack, de L Horne, & Sheather, 1988), the effects of rTMS on implicit, sub-conscious measures of AN symptoms i.e. attentional bias tasks may be more informative (Renwick, Campbell, & Schmidt, 2013). Moreover, previous rTMS studies in ED have looked at the effects of rTMS on food cravings, which could be argued as an ED symptom that fluctuates more than others. Therefore, the core symptoms of AN assessed here (urge to restrict, feeling full and fat) may not be as susceptible to short-term modulation with rTMS as symptoms such as food cravings. The additional VAS, e.g. regarding mood were only administered as part of the FCT, therefore we could not control for baseline levels across these measures and finally, in terms of blinding success, we did not titrate choices for the researcher based on previous answers and this led to results indicating that researcher blinding was not effective.

Future directions

In elucidating the therapeutic potential of rTMS in AN, particularly in relation to severe cases, repeated session designs may be more informative than single-session, exploratory studies. Given the persistent nature of AN symptoms and the accumulative, neuroplasticity effects proposed to underlie rTMS, single-session studies provide limited information on the long-term benefits of such techniques and their potential as treatment adjuncts for ED. However, the findings reported here pave the way for future, therapeutic RCT of rTMS in AN.

Given the range of neuromodulation techniques that are available, and the large degree of protocol variability within each, there is a great deal of scope for more neuromodulation research in AN. For example, whilst we targeted the left DLPFC with HF rTMS to alter core AN symptoms, others have suggested alternative protocols; left-sided tDCS protocols have been proposed in an attempt to restore a hypothesised inter-hemispheric imbalance in AN (Hecht, 2010) and preliminary findings are promising (Khedr, Elfetoh, et al., 2014). Equally so, LF rTMS to the right DLPFC may more directly modulate right-sided hyperactivity often proposed to underlie AN (Grunwald, Weiss, Assmann, & Ettrich, 2004; Seeger, Braus, Ruf, Goldberger, & Schmidt, 2002; Uher et al., 2003). In addition, targeting right parietal regions with rTMS has been suggested as a way of modulating body dysmorphia in AN (Bainbridge & Brown, 2014). Moreover, despite being a more invasive procedure, DBS to areas such as the cingulate cortex and nucleus accumbens has shown promising results in improving AN symptoms (Lipsman et al., 2013; McLaughlin et al., 2013; Treasure & Schmidt, 2013; Wu et al., 2013).

Optimising neuromodulation devices, stimulation targets, the dose and duration of neuromodulation protocols in the treatment of all ED require further clarification (Tsai, 2005). Moreover, there is a need to identify biomarkers in order to understand disease mechanisms, guide future neuromodulation research and explore the mechanisms underlying brain-directed interventions. This is most likely to arise from protocols that incorporate neuroimaging modalities (Fidalgo et al., 2014).

Summary

These findings suggest that compared to sham, participants who received a single-session of neuronavigated real rTMS report reduced AN symptoms. These effects were not accompanied by similar improvements in mood and anxiety. Importantly, the blinding procedure within participants, i.e. the concealment of intervention allocation, was only partially successful.

Chapter 3.4 The effects of repetitive transcranial magnetic stimulation on food preference and consumption in anorexia nervosa

People with AN demonstrate altered food preferences and often display strong emotional aversions in response to food and eating. Compared to their healthy counterparts, they both explicitly and implicitly report reduced 'liking' (hedonic/pleasure) and 'wanting' (incentive/motivation) of food which unsurprisingly, is most pronounced in relation to high-calorie foods (Cowdrey, Finlayson, & Park, 2013; Jiang, Soussignan, Rigaud, & Schaal, 2010; Spring & Bulik, 2014). Distinct brain circuitry has been reported in relation to the liking and wanting of food and has been implicated in the aetiology of ED (Berridge, 2009; Castro & Berridge, 2014). Specifically, neuroimaging data suggests a dysfunctional response to food-related cues and other salient stimuli is associated with altered neural activity in mesolimbic regions such as the insula, amygdala and anterior cingulate cortex (Cowdrey et al., 2011; Holsen et al., 2012) in conjunction with excessive activation of cognitive control areas such as the PFC (Brooks et al., 2011; Holsen et al., 2012; Park et al., 2014; Santel et al., 2006). These differences in neural circuitry have been suggested to be both state and trait related and are proposed to contribute to the impaired food motivation and appetite regulation which are characteristic of AN (Holsen et al., 2012; Kaye et al., 2009; Lipsman et al., 2014; van Kuyck et al., 2009).

Similarly, altered neurocircuitry has been proposed to underlie other ED such as BN and BED (Brooks et al., 2011; Frank et al., 2006; Schienle et al., 2009). The neurobiological correlates of food craving and resulting impulse control difficulties in BN, BED and obesity have been likened to the neural underpinnings of substance dependence. Specifically, increased activity in the orbitofrontal cortex, amygdala and insula have been linked to food cravings (Tang et al., 2012; Wang et al., 2004), whilst reduced prefrontal activation has been reported in reaction to both food cues and during inhibitory control tasks in BN (Joos, Saum, Zeeck, et al., 2011), BED (Hege et al., 2014) and obese individuals (Kishinevsky et al., 2012).

Neuromodulation techniques have the ability to alter neural activity and thus offer potential for modulating the neural circuitry that underlies salience attribution and motivational processes towards food and eating. For example, in healthy individuals, LF rTMS to the right DLPFC decreased the value assigned to food (Camus et al., 2009), whilst in people who report frequent food cravings, HF rTMS to the left DLPFC, prevented cravings during a food exposure task (Uher, Yoganathan, et al., 2005). Barth et al. (2011), however, did not to replicate these results using improved sham rTMS in a crossover design, but several other studies have reported reduced food cravings following anodal/excitatory tDCS to the right DLPFC and this is most pronounced in relation to sweet foods (Fregni et al., 2008; Goldman et al., 2011; Kekic et al., 2014). Similar findings with HF rTMS to the left DLPFC extend to clinical populations; reductions in the desire to eat were reported following tDCS in obese individuals (Montenegro et al., 2012) and rTMS in BN (Van den Eynde et al., 2010).

Food cravings and resulting binge-eating episodes are core components of ED such as binge/purge AN, BN and BED, however they fluctuate diurnally (van der Ster Wallin, Norring, & Holmgren, 1994) and often depend on factors such as mood (Hill, Weaver, & Blundell, 1991) and menstrual cycle (Cohen, Sherwin, & Fleming, 1987). In contrast, core AN symptoms, such as extreme food restriction and pathological fear of weight gain, are stubborn and arguably less resistant to quotidian change. Whilst evidence for short-term effects of neuromodulation on such AN symptoms exists (see Chapter 3.3 and Van den Eynde, Guillaume, et al., 2013), it could be argued that these pathologies are unlikely to alter markedly without intense and repeated neuromodulation exposure which has been reported in other therapeutic designs (Kamolz et al., 2008; Khedr, Elfetoh, et al., 2014; McClelland, Bozhilova, Nestler, et al., 2013). However, since the neurocircuitry underlying hedonic and motivational processes towards food have been reported to be altered by neuromodulation, it may be possible to temporarily alter the characteristic food aversions seen in AN.

Whilst neuromodulation research in relation to both food and drugs has shown potential in reducing cravings (Jansen et al., 2013), the variety of

neuromodulation protocols and techniques available are also likely to be able to induce the opposite effects, i.e. increase the preference towards such substances. For example, increases in cravings for methamphetamine have been reported following LF rTMS to the left DLPFC (Li, Malcolm, et al., 2013), whilst HF rTMS to the superior frontal gyrus increased cravings for cigarettes/nicotine in smokers (Rose et al., 2011). Moreover, increases in eating-related outcomes have been demonstrated following neuromodulation; specifically, DBS to the sub-thalamic nucleus in people with Parkinson's disease and DBS to various areas of both the hypothalamus and nucleus accumbens in animals, has led to significant increases in body weight and food intake respectively (see Chapter 2 or McClelland, Bozhilova, Campbell, et al., 2013).

In summary, individuals with AN exhibit dysfunctional neural activity that is likely to underlie reduced hedonic experiences and motivation towards food and eating. Neuromodulation has reported effects on the value attributed to food cues and food cravings and therefore may offer potential in subliminally improving attitudes and preferences towards food in people with AN. Importantly, hedonic hunger has been shown to predict weight gain in AN (Witt & Lowe, 2014) and therefore implicitly altering food preference may facilitate food intake in AN and have implications for treatment.

The aim of the research reported in this chapter is to examine whether following a food-cue exposure task, real rTMS affects food preferences and food consumption in AN. We hypothesised that real rTMS, compared to sham, would temporarily increase the liking of food in individuals with AN and subsequently lead to increased food consumption.

Methods

Participants

Recruitment and randomisation procedure are described in Chapter 3.2.

Procedures

A description of procedures is provided in Chapter 3.2.

Measures

Baseline

The baseline measures are described in Chapter 3.3.

Outcome measures

Preference for each of the food types (chocolate, crisps, nuts, biscuits) was measured with 10cm VAS pre (TP2) and post-rTMS (TP3) across four domains – perceived smell, taste, appearance and urge to eat (see Appendix G.3). Scores were combined into an overall ‘liking’ variable for each food type, with a total possible score of 40. Scores across the individual VAS (perceived smell, taste, appearance and urge to eat) for each food type were also examined.

Two measures were used to assess the effects of rTMS on food consumption in AN; the amount of smoothie consumed immediately after real/sham rTMS, and how much participants ate during the 24 hours following stimulation. With regards to smoothie consumption, at the end of the rTMS testing session, participants were asked to choose one of three flavours (mango/banana, strawberry/banana or kiwi fruit) of a well-known Innocent® fruit smoothie. Participants were then asked to ‘drink as much as you can’ of the chosen flavour and left alone in the room for approximately 10 minutes. The amount of smoothie drunk was established by measuring the weight of the smoothie (in grams) before and after consumption. To establish how much participants ate during the 24 hours after real/sham rTMS, during the follow-up call, they were asked to indicate how much they had eaten in the past 24 hours by giving a number between 1 (no meals) and 10 (all meals; 3 main meals and 3 snacks).

Statistical analyses

Statistical analyses were performed using IBM® SPSS® software (Version 22). Following consultation with a statistician, when normality or other ANOVA assumptions such as homogeneity of were violated (assessed via Kolmogorov-Smirnov and Levene’s test statistics respectively) log transformations or other non-parametric alternatives were employed. When Mauchly’s test of sphericity

was violated, Greenhouse-Geisser corrections are reported. All tests were two-tailed and the level of significance was set at $\alpha = 0.05$.

Following the first administration of the FCT, correlations regarding the whole sample were conducted in order to examine the relationship between the composite outcomes, individual and additional VAS and the food related outcomes (mentioned above in Chapter 3.3).

The effect of real versus sham rTMS on the liking of each of the different foods (primary outcome), along with the individual food VAS listed above, was evaluated using a mixed ANOVA (group: real/sham rTMS x time: TP2, TP3). Additionally, post-hoc correlational analyses were conducted separately for each real/sham rTMS groups to examine associations between primary and secondary outcomes and changes to food ratings following real/sham rTMS. The effect of real versus sham rTMS on both smoothie consumption and amount of food eaten was evaluated using independent t-tests.

Partial eta squared (η^2) and Cohen's d effect sizes are reported for mixed ANOVAs and t-tests respectively. Partial eta squared is automatically computed within SPSS by dividing the sums of squares for the effect of interest by the total sums of squares i.e. $\eta^2 = SS_{between}/SS_{total}$ (Levine & Hullett, 2002). Cohen's d was computed by dividing the difference in means by the pooled standard deviation i.e. $d = M_1 - M_2/\sqrt{(SD_1^2 + SD_2^2)/2}$. Interpretation of the magnitude of η^2 is 0.01-0.06 = small; 0.06-0.14 = medium and > 0.14 ; large; and for Cohen's d effect sizes 0.15-0.40 = small; 0.4-0.75 = medium and > 0.75 : large (Cohen, 1988).

Results

The same 49 right-handed, female individuals described above (Chapter 3.3), randomised to real ($n = 21$, restrictive-AN = 13, binge/purge-AN = 8) and sham ($n = 28$, restrictive-AN = 15, binge/purge-AN = 13) were included in the subsequent analyses.

Baseline characteristics

Baseline characteristics are described in Chapter 3.3 and presented in Table 3.2.

Outcomes

Following the first FCT, Pearson's correlations including the entire sample indicated no significant correlations between the liking of different foods and either the composite core AN symptoms or the anxiety/stress measure. However, there was a positive association between the overall liking of chocolate and current state of hunger [$r = 0.38, p = 0.009$] and urge to eat [$r = 0.37, p = 0.009$]. Similarly, there was a positive association between the urge to eat and liking of biscuits [$r = 0.34, p = 0.017$]. Finally, the liking of crisps was positively correlated with current hunger [$r = 0.37, p = 0.010$] and urge to eat [$r = 0.44, p = 0.001$].

Liking of foods

No significant interaction effects, differences across time or between groups were found in relation to liking of chocolate, crisps or nuts (see Table 3.8). There was however, a significant interaction between stimulation type and time in relation to liking biscuits; sham rTMS reduced the liking, while real rTMS increased it (Table 3.8). This was predominantly driven by a significant interaction for the urge to eat (Table 3.12) the biscuits and their perceived taste (Table 3.11), alongside an interaction trend regarding their appearance (Table 3.9). In other words, following real rTMS, participants had a stronger urge to eat the biscuits, which were perceived as tastier and which looked more appetising. In contrast, there was an opposite effect in relation to the perceived taste of chocolate; real rTMS reduced the perceived taste of chocolate, i.e. participants rated chocolate as less tasty, more so than sham rTMS (Table 3.11). There were no group, time or interaction effects in relation to the perceived smell of each food type (Table 3.10).

Table 3.7 Mixed ANOVA results of the composite ‘liking of food’ outcomes following real/sham rTMS. Mean \pm SD reported.

	Time Point	Real rTMS (<i>n</i> = 21)	Sham rTMS (<i>n</i> = 28)	ANOVA Time	ANOVA Group	ANOVA INTERACTION Group x Time
Chocolate	Post FCTpre/pre rTMS (TP2)	14.59 \pm 7.51	18.44 \pm 11.60	<i>F</i> (1) = 0.01 <i>p</i> = 0.911	<i>F</i> (1) = 2.13 <i>p</i> = 0.151	<i>F</i> (1) = 0.15 <i>p</i> = 0.703
	Post rTMS & FCTpost (TP3)	14.14 \pm 9.84	18.68 \pm 11.41	η^2 = 0.00	η^2 = 0.04	η^2 = 0.00
Crisps	Post FCTpre/pre rTMS (TP2)	12.07 \pm 10.05	14.54 \pm 9.78	<i>F</i> (1) = 0.87 <i>p</i> = 0.355	<i>F</i> (1) = 0.54 <i>p</i> = 0.468	<i>F</i> (1) = 0.13 <i>p</i> = 0.716
	Post rTMS & FCTpost (TP3)	13.59 \pm 10.91	15.20 \pm 10.73	η^2 = 0.02	η^2 = 0.01	η^2 = 0.00
Nuts	Post FCTpre/pre rTMS (TP2)	14.27 \pm 9.04	9.87 \pm 8.61	<i>F</i> (1) = 0.48 <i>p</i> = 0.493	<i>F</i> (1) = 2.71 <i>p</i> = 0.107	<i>F</i> (1) = 0.07 <i>p</i> = 0.787
	Post rTMS & FCTpost (TP3)	13.53 \pm 10.61	11.20 \pm 9.50	η^2 = 0.01	η^2 = 0.06	η^2 = 0.00
Biscuits	Post FCTpre/pre rTMS (TP2)	15.30 \pm 10.76	16.18 \pm 12.43	<i>F</i> (1) = 0.07 <i>p</i> = 0.792	<i>F</i> (1) = 0.06 <i>p</i> = 0.810	<i>F</i> (1) = 7.63 <i>p</i> = 0.008
	Post rTMS & FCTpost (TP3)	17.16 \pm 11.56	14.65 \pm 12.02	η^2 = 0.00	η^2 = 0.00	η^2 = 0.14

The composite ‘liking of food’ outcome was computed by adding scores across all four 10cm visual analogue scales relating to the perceived appearance, smell, taste and urge to eat each food type. Therefore, scores on this composite ‘liking of food’ outcome could range from 0 to 40.

Table 3.8 Mixed ANOVA results of the ‘appearance’ of each food type following real/sham rTMS. Mean \pm SD reported.

	Time Point	Real rTMS (<i>n</i> = 21)	Sham rTMS (<i>n</i> = 28)	ANOVA Time	ANOVA Group	ANOVA INTERACTION Group x Time
Chocolate	Post FCTpre/pre rTMS (TP2)	3.63 \pm 2.81	4.74 \pm 3.53	<i>F</i> (1) = 0.15 <i>p</i> = 0.701 η^2 = 0.00	<i>F</i> (1) = 1.99 <i>p</i> = 0.165 η^2 = 0.04	<i>F</i> (1) = 0.11 <i>p</i> = 0.739 η^2 = 0.00
	Post rTMS & FCTpost (TP3)	3.64 \pm 3.13	4.98 \pm 3.18			
Crisps	Post FCTpre/pre rTMS (TP2)	2.72 \pm 2.79	3.17 \pm 2.94	<i>F</i> (1) = 2.94 <i>p</i> = 0.093 η^2 = 0.06	<i>F</i> (1) = 0.21 <i>p</i> = 0.650 η^2 = 0.00	<i>F</i> (1) = 0.07 <i>p</i> = 0.796 η^2 = 0.00
	Post rTMS & FCTpost (TP3)	3.43 \pm 2.94	3.69 \pm 3.19			
Nuts	Post FCTpre/pre rTMS (TP2)	3.75 \pm 2.67	2.26 \pm 2.49	<i>F</i> (1) = 0.00 <i>p</i> = 0.975 η^2 = 0.00	<i>F</i> (1) = 4.29 <i>p</i> = 0.044 η^2 = 0.08	<i>F</i> (1) = 0.00 <i>p</i> = 0.991 η^2 = 0.00
	Post rTMS & FCTpost (TP3)	3.73 \pm 3.06	2.25 \pm 2.47			
Biscuits	Post FCTpre/pre rTMS (TP2)	3.87 \pm 3.22	4.07 \pm 3.52	<i>F</i> (1) = 0.04 <i>p</i> = 0.835 η^2 = 0.00	<i>F</i> (1) = 0.03 <i>p</i> = 0.855 η^2 = 0.00	<i>F</i> (1) = 3.75 <i>p</i> = 0.059 η^2 = 0.07
	Post rTMS & FCTpost (TP3)	4.28 \pm 3.19	3.74 \pm 3.24			

Appearance of each food type was measured on a 10cm visual analogue scale; scores could range from 0 (not appetising at all) to 10 (extremely appetising).

Table 3.9 Mixed ANOVA results of the perceived ‘smell’ of each food type following real/sham rTMS. Mean \pm SD reported.

	Time Point	Real rTMS (<i>n</i> = 21)	Sham rTMS (<i>n</i> = 28)	ANOVA Time	ANOVA Group	ANOVA INTERACTION Group x Time
Chocolate	Post FCTpre/pre rTMS (TP2)	3.30 \pm 2.74	3.97 \pm 3.61	<i>F</i> (1) = 0.66 <i>p</i> = 0.420 η^2 = 0.01	<i>F</i> (1) = 0.46 <i>p</i> = 0.502 η^2 = 0.01	<i>F</i> (1) = 0.06 <i>p</i> = 0.808 η^2 = 0.00
	Post rTMS & FCTpost (TP3)	3.70 \pm 3.01	4.18 \pm 3.31			
Crisps	Post FCTpre/pre rTMS (TP2)	3.24 \pm 2.87	3.93 \pm 3.02	<i>F</i> (1) = 0.79 <i>p</i> = 0.378 η^2 = 0.02	<i>F</i> (1) = 0.49 <i>p</i> = 0.486 η^2 = 0.01	<i>F</i> (1) = 0.14 <i>p</i> = 0.710 η^2 = 0.00
	Post rTMS & FCTpost (TP3)	3.78 \pm 3.07	4.16 \pm 3.01			
Nuts	Post FCTpre/pre rTMS (TP2)	3.77 \pm 3.05	2.50 \pm 2.66	<i>F</i> (1) = 0.11 <i>p</i> = 0.740 η^2 = 0.00	<i>F</i> (1) = 1.99 <i>p</i> = 0.164 η^2 = 0.04	<i>F</i> (1) = 0.45 <i>p</i> = 0.505 η^2 = 0.01
	Post rTMS & FCTpost (TP3)	3.69 \pm 3.17	2.73 \pm 2.52			
Biscuits	Post FCTpre/pre rTMS (TP2)	4.29 \pm 3.30	3.88 \pm 3.47	<i>F</i> (1) = 0.17 <i>p</i> = 0.685 η^2 = 0.00	<i>F</i> (1) = 0.64 <i>p</i> = 0.429 η^2 = 0.01	<i>F</i> (1) = 2.20 <i>p</i> = 0.145 η^2 = 0.05
	Post rTMS & FCTpost (TP3)	4.70 \pm 3.18	3.64 \pm 3.12			

The perceived smell of each food type was measured on a 10cm visual analogue scale; scores could range from 0 (not appetising at all) to 10 (extremely appetising).

Table 3.10 Mixed ANOVA results of the perceived ‘taste’ of each food type following real/sham rTMS. Mean \pm SD reported.

	Time Point	Real rTMS (<i>n</i> = 21)	Sham rTMS (<i>n</i> = 28)	ANOVA Time	ANOVA Group	ANOVA INTERACTION Group x Time
Chocolate	Post FCTpre/pre rTMS (TP2)	5.78 \pm 2.77	6.30 \pm 2.97	<i>F</i> (1) = 7.57 <i>p</i> = 0.008 η^2 = 0.14	<i>F</i> (1) = 1.60 <i>p</i> = 0.211 η^2 = 0.03	<i>F</i> (1) = 3.87 <i>p</i> = 0.055 η^2 = 0.08
	Post rTMS & FCTpost (TP3)	4.50 \pm 3.19	6.08 \pm 3.22			
Crisps	Post FCTpre/pre rTMS (TP2)	4.23 \pm 3.32	4.86 \pm 3.11	<i>F</i> (1) = 0.38 <i>p</i> = 0.540 η^2 = 0.01	<i>F</i> (1) = 0.69 <i>p</i> = 0.409 η^2 = 0.01	<i>F</i> (1) = 0.07 <i>p</i> = 0.790 η^2 = 0.00
	Post rTMS & FCTpost (TP3)	3.93 \pm 3.22	4.74 \pm 3.17			
Nuts	Post FCTpre/pre rTMS (TP2)	4.59 \pm 2.93	3.43 \pm 2.79	<i>F</i> (1) = 4.44 <i>p</i> = 0.041 η^2 = 0.09	<i>F</i> (1) = 2.10 <i>p</i> = 0.154 η^2 = 0.04	<i>F</i> (1) = 0.07 <i>p</i> = 0.797 η^2 = 0.00
	Post rTMS & FCTpost (TP3)	3.95 \pm 2.87	2.93 \pm 2.57			
Biscuits	Post FCTpre/pre rTMS (TP2)	4.92 \pm 3.20	5.23 \pm 3.23	<i>F</i> (1) = 2.47 <i>p</i> = 0.123 η^2 = 0.05	<i>F</i> (1) = 0.01 <i>p</i> = 0.908 η^2 = 0.00	<i>F</i> (1) = 8.21 <i>p</i> = 0.006 η^2 = 0.15
	Post rTMS & FCTpost (TP3)	5.11 \pm 3.23	4.59 \pm 3.34			

The perceived taste of each food type was measured on a 10cm visual analogue scale; scores could range from 0 (not tasty at all) to 10 (extremely tasty).

Table 3.11 Mixed ANOVA results of the ‘urge to eat’ each food type following real/sham rTMS. Mean \pm SD reported.

	Time Point	Real rTMS (<i>n</i> = 21)	Sham rTMS (<i>n</i> = 28)	ANOVA Time	ANOVA Group	ANOVA INTERACTION Group x Time
Chocolate	Post FCTpre/pre rTMS (TP2)	1.88 \pm 1.99	3.43 \pm 3.59	<i>F</i> (1) = 0.38 <i>p</i> = 0.541 η^2 = 0.01	<i>F</i> (1) = 3.04 <i>p</i> = 0.088 η^2 = 0.06	<i>F</i> (1) = 0.34 <i>p</i> = 0.564 η^2 = 0.00
	Post rTMS & FCTII (TP3)	2.31 \pm 2.37	3.44 \pm 3.14			
Crisps	Post FCTpre/pre rTMS (TP2)	1.89 \pm 2.57	2.57 \pm 2.95	<i>F</i> (1) = 0.78 <i>p</i> = 0.382 η^2 = 0.02	<i>F</i> (1) = 0.33 <i>p</i> = 0.567 η^2 = 0.01	<i>F</i> (1) = 0.60 <i>p</i> = 0.443 η^2 = 0.01
	Post rTMS & FCTII (TP3)	2.45 \pm 2.70	2.61 \pm 2.76			
Nuts	Post FCTpre/pre rTMS (TP2)	1.81 \pm 2.02	1.68 \pm 2.21	<i>F</i> (1) = 0.88 <i>p</i> = 0.353 η^2 = 0.02	<i>F</i> (1) = 0.54 <i>p</i> = 0.468 η^2 = 0.01	<i>F</i> (1) = 1.26 <i>p</i> = 0.267 η^2 = 0.03
	Post rTMS & FCTII (TP3)	2.37 \pm 2.78	1.63 \pm 1.97			
Biscuits	Post FCTpre/pre rTMS (TP2)	2.21 \pm 2.85	3.01 \pm 3.23	<i>F</i> (1) = 0.95 <i>p</i> = 0.334 η^2 = 0.02	<i>F</i> (1) = 0.05 <i>p</i> = 0.816 η^2 = 0.00	<i>F</i> (1) = 4.85 <i>p</i> = 0.033 η^2 = 0.09
	Post rTMS & FCTII (TP3)	3.06 \pm 3.17	2.68 \pm 3.31			

The urge to eat each food type was measured on a 10cm visual analogue scale; scores could range from 0 (would not wish to eat them at all) to 10 (would like to eat some very much).

Pearson's post-hoc correlations were conducted separately for each real/sham rTMS groups regarding food preferences and both composite and individual VAS outcomes following rTMS. Following real rTMS, level of hunger was associated with the liking of biscuits [$r = 0.63, p = 0.002$] and nuts [$r = 0.64, p = 0.002$]. Similarly, current urge to eat was positively associated with the liking of chocolate [$r = 0.44, p = 0.048$] and crisps [$r = 0.43, p = 0.050$]. Following sham rTMS, the liking of nuts was positively correlated with both levels of feeling full [$r = 0.45, p = 0.015$] and core AN symptoms [$r = 0.44, p = 0.018$]. Negative correlations were observed following sham rTMS between levels of feeling fat and the liking of biscuits [$r = -0.45, p = 0.015$], and between mood and the liking of crisps [$r = -0.47, p = 0.012$].

Food consumption

There were no significant differences between groups in either the amount of smoothie consumed [$t(47) = -0.14, p = 0.887, d = 0.04$] (see Figure 3.6) or the amount of food eaten during the 24 hours following real/sham rTMS [$t(47) = -0.21, p = 0.831, d = 0.06$] (see Figure 3.7).

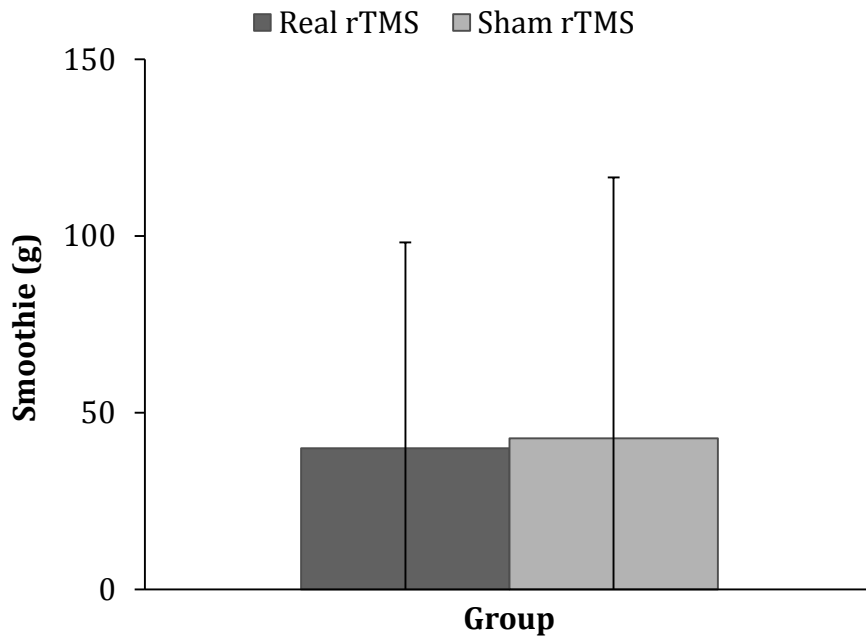


Figure 3.6 Amount of smoothie consumed after real/sham rTMS. Mean \pm SD reported

The mean \pm SD values for the amount of smoothie (g) consumed in the real and sham groups are 40.00 ± 58.24 and 42.78 ± 73.79 respectively.

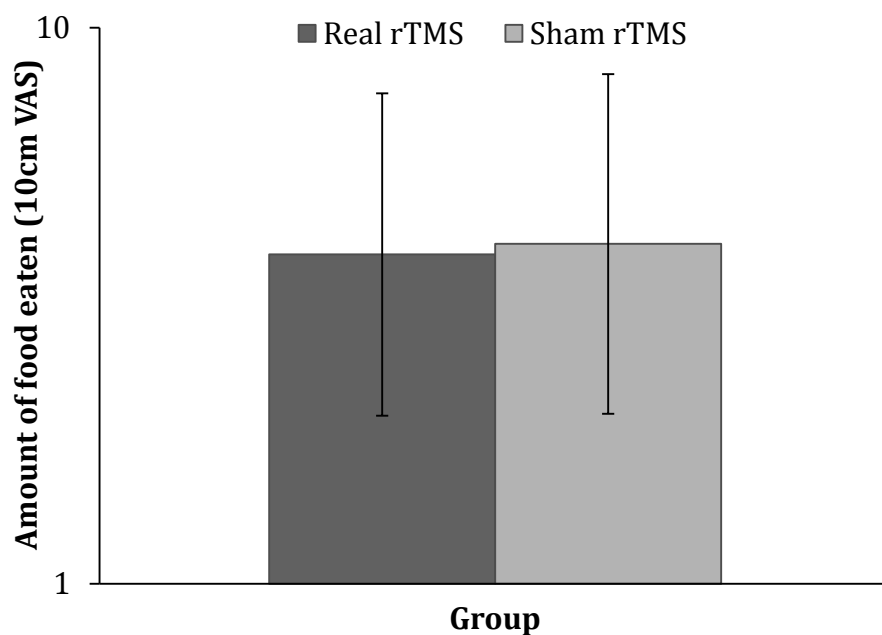


Figure 3.7 Amount of food eaten during the 24 hours following real/sham rTMS. Mean \pm SD reported.

Scores ranged from 1 (no meals) to 10 (all meals i.e. 3 main meals and 3 snacks) on a 10cm visual analogue scale (VAS). The mean \pm SD values for the amount of food in the real and sham groups are 6.33 ± 2.61 and 6.50 ± 2.75 respectively.

Discussion

The findings support our hypothesis; real rTMS increased the liking of some foods in AN whilst liking of food was reduced following sham rTMS. However, the increased preference was food-specific and only in relation to the liking of sweet biscuits, and not chocolate, crisps or nuts. Moreover, changes in the liking of biscuits were positively associated with hunger, and negatively associated with levels of feeling fat in the real and sham groups respectively. The increased preference for food following real rTMS was not associated with any subsequent increase in food consumption.

The data are in part agreement with existing literature that suggests the liking of (some) sweet foods can be modulated by neuromodulation. Reduced food cravings, in particular in relation to sweet foods, have been reported following tDCS in frequent food cravers (Fregni et al., 2008; Goldman et al., 2011; Kekic et al., 2014). Moreover, our findings are in line with other research that suggests neuromodulation can also increase the liking and wanting of substances such as alcohol, nicotine and food (Li, Malcolm, et al., 2013; Rose et al., 2011). Whilst hunger has not been reported to be altered following rTMS in AN (see Chapter 3.3 and Van den Eynde, Guillaume, et al., 2013), it was positively correlated with the liking of biscuits within this sample.

Hemispheric lateralisation

Differences between literature demonstrating reduced food cravings, and our findings of increased liking of food in AN, may be due to differences between the neuromodulation protocols used. For example, the tDCS anode right/cathode left studies predominantly activate the right PFC, whilst HF rTMS to the left DLPFC activates the left PFC. Research suggests that neuromodulation has opposing effects on the contralateral hemisphere to that which is stimulated (Fox et al., 1997) i.e. excitatory rTMS to the left DLPFC may inhibit activity in the right DLPFC and vice versa. If this is the case, anode right/cathode left tDCS and HF (excitatory) rTMS to the left DLPFC would have opposite effects on neural

activity and may explain the difference in the reported effects on the liking of food outcomes.

Sample

The opposing effects on food preferences might also be due to the different groups of individuals studied. Different neural mechanisms have been proposed to underlie ED related problems that involve food cravings and poor inhibitory control (e.g. AN binge/purge, BN, BED and obesity) and the core characteristics of restrictive AN (characterised by impaired hedonic appetite drives and excessive cognitive control over food). This is hard to disentangle in the current study that has both restrictive and binge/purge AN subtypes. For example, impaired right prefrontal activity has been implicated in over-eating syndromes such as obesity (Alonso-Alonso & Pascual-Leone, 2007) and therefore, anodal tDCS may remotely alter reward-related neural circuits (Fregni et al., 2008) and improve cognitive control over food cravings. In comparison, rTMS to the left DLPFC may remotely alter limbic, food-motivation related circuitry in AN that is involved in hedonic appetite (Holsen et al., 2012) e.g. by increasing reported prefrontal hypoperfusion in AN (Frank et al., 2004).

Strengths

This is the first study to utilise food exposure tasks in ED neuromodulation research. Hedonic hunger is reduced in AN, yet predicts weight gain (Witt & Lowe, 2014), therefore it is an important construct that is worth investigating in AN. Additionally, mentioned previously, this study followed a robust randomised control protocol and employs improved rTMS methodologies such as the MEP method of estimating MT and neuronavigation.

Limitations

Unlike the main outcomes measured in Chapter 3.3, the effects of rTMS on food preferences were only assessed immediately before and after real/sham rTMS. Therefore, the findings are limited by the fact that the study did not control for baseline levels of the liking of food. The effect of rTMS on food consumption is probably limited by social desirability effects – the amount of smoothie drunk

and reported food intake following real/sham rTMS is likely to have been influenced by the experimental setting. Furthermore, the limited way in which food intake during the 24 hours following rTMS was assessed was a blunt measure. Finally, whilst some of the binge/purge subtype participants informally reported binge-eating episodes post rTMS, this was not formally assessed.

Future directions

Given the opposing findings relating to the effects of rTMS towards different sweet foods (chocolate/biscuits) and existing evidence for distinct neural responses to chocolate and its addictive properties (Hetherington & MacDiarmid, 1993; Macdiarmid & Hetherington, 1995; Sokolov, Pavlova, Klosterhalfen, & Enck, 2013), future research may wish to explore the neural mechanisms underlying specific food cues in AN more thoroughly. This might perhaps be accomplished by comparing the effects of excitatory (HF rTMS/anodal tDCS) and inhibitory (LF rTMS/cathodal tDCS) neuromodulation on food related ratings in AN. Moreover, the use of online exposure tasks i.e. during neuromodulation rather than immediately before/after, that are more salient and realistic than those employed here, may elicit stronger effects on hedonic ratings of food in AN. Finally, virtual reality based food consumption tasks may elicit more interesting and accurate findings regarding potential food intake immediately after rTMS that is not as limited by unnatural experimental settings. Similarly, a food diary outlining the type and amount of food consumed in the 24 hours following rTMS may provide more informative findings regarding nutritional/calorie content consumed and binge/purge episodes.

Summary

Data suggest that real and sham rTMS have opposite effects on the liking of specific foods in AN; real rTMS increases whilst sham rTMS decreases the liking of sweet biscuits. This finding was associated with levels of hunger and feeling fat i.e. increased levels of hunger and feeling fat were positively and negatively associated with the liking of biscuits following real/sham rTMS respectively. However, real rTMS was not associated with increased food consumption.

Chapter 3.5 The effects of repetitive transcranial magnetic stimulation on salivary cortisol concentrations in anorexia nervosa

Investigating the usefulness of neuromodulation techniques as treatment adjuncts in psychiatry is timely and important. However, there is an equally strong need to investigate the neurobiological mechanisms underlying neuromodulation, as a means of understanding both disease and therapeutic mechanisms. In their systematic review, Fidalgo et al. (2014) emphasise the importance of investigating the relationship between biomarkers and clinical response to non-invasive neuromodulation in depression. Whilst they found that various biomarkers investigated with neuroimaging modalities positively correlated with clinical improvements, peripheral levels of BDNF were the strongest predictor of treatment response. Other neuroendocrinological responses, e.g. hypothalamic-pituitary-adrenal (HPA) axis activity (cortisol concentrations) have been examined to explore the effects of rTMS. The HPA axis plays a central role in regulating the body's response to stressful situations. Corticotrophin-releasing hormone from the hypothalamus causes secretion of the adrenocorticotrophic hormone from the pituitary gland and this in turn stimulates secretion of glucocorticoids, namely cortisol, from the adrenal cortex. This regulates the body's physiological and behavioural response to stress (Charmandari, Tsigos, & Chrousos, 2005). The PFC has been implicated in HPA axis activity (McKlveen et al., 2013) and therefore examining the effects of prefrontal rTMS on cortisol concentrations may help to clarify the role of HPA activity in psychiatric disorders, and to determine whether alterations to the HPA axis underlie the therapeutic mechanisms of neuromodulation. However, changes in cortisol levels may not be simple to interpret as, for example, a change could be the result of either alterations to the PFC or the individuals perception of the rTMS as something unpleasant/stressful.

Early animal studies suggest that rTMS alters HPA axis activity (Hedges et al., 2003). More recently, in healthy but experimentally stress-induced humans, HF rTMS to the left DLPFC was shown to reduce salivary cortisol concentrations

and thus attenuate HPA activity (Baeken et al., 2014). The same group have also reported similar findings in depression (Baeken et al., 2009), a neuro-circuit based psychiatric disorder that is associated with increased HPA activity (Swaab, Bao, & Lucassen, 2005). The reported decrease in cortisol suggests that the intervention is not perceived as very stressful and hence the decrease in cortisol may be a direct effect of the rTMS on the PFC.

Both BN and AN are associated with HPA hyperactivity/hypercortisolemia (for reviews see Licinio, Wong, & Gold, 1996; Lo Sauro, Ravaldi, Cabras, Faravelli, & Ricca, 2008). In relation to AN, HPA axis hyperactivity is independent of comorbid psychopathology and associated with weight loss and illness severity. Moreover, evidence suggests trait related HPA axis disturbances in AN, given that alterations exist following weight restoration (Lo Sauro et al., 2008). In fact, alterations in the HPA axis have been proposed to be causally involved in the development of AN (Connan et al., 2003; Connan et al., 2007). Lawson et al. (2013) have also reported associations between HPA hyperactivity, homeostatic and hedonic appetite suppression and hypoactivity of food motivation circuitry in AN.

Despite evidence that cortisol concentrations are modulated following rTMS and ED are associated with HPA hyperactivity, only one study has examined the effects of rTMS on cortisol concentration in ED. Compared to sham, real HF rTMS, applied to the left DLPFC, was associated with reduced salivary cortisol levels in BN (Claudino et al., 2011). Given such findings and the well-documented HPA hyperactivity in AN, this chapter describes an examination of the effects of rTMS on salivary cortisol concentrations in AN. It was hypothesised that compared to sham, real rTMS would reduce salivary cortisol concentrations in individuals with AN.

Methods

Participants

Recruitment and randomisation procedure are described in Chapter 3.2. Gender and time of day are confounding factors in studies involving cortisol measures.

However, all participants in the RCT were female and underwent the rTMS testing session in the afternoon. Therefore, the same 51 individuals described previously were considered.

Procedures

A description of procedures is provided in Chapter 3.2.

Measures

Baseline

The baseline measures are described in Chapter 3.3.

Outcomes

Participants were requested to refrain from eating for 1 hour prior to the visit. Salivette® (Sarstedt, Germany) devices were used to collect saliva samples. Appendix H.3 contains a leaflet by Sarstedt with guidance on how to obtain a saliva sample. Participants were instructed not to touch the cotton (as this may have an impact on the quality of the sample) and to chew for around 30 seconds. Participants were also not allowed to rinse their mouth with any fluid prior or post sample collection. This is a common adaptation that has been reported by other research groups (Gustafsson, Janlert, Theorell, & Hammarstrom, 2010).

Saliva samples were collected at five time points during the experiment (see Table 3.1); at the start of the session (S1), following the first FCT (S2), immediately following real/sham rTMS (S3), after the second FCT (S4) and at the end of the testing session (S5). Samples were stored at -20°C where they are stable for several months. The frozen samples were thawed and the saliva separated from the swab by centrifugation (1500g, 15 min). Cortisol concentrations were measured by enzyme-linked immunosorbent assay ELISA (Salimetrics, Germany). Tracy Dew from Viapath pathology services, King's College Hospital conducted these procedures of centrifugation and cortisol concentration measurement.

Statistical analysis

Statistical analyses were performed using IBM® SPSS® software (Version 22). When normality or other ANOVA assumptions such as homogeneity of variance were violated (assessed via Kolmogorov-Smirnov and Levene's test statistics respectively) log transformations or other non-parametric alternatives were employed. When Mauchly's test of sphericity was violated, Greenhouse-Geisser corrections are reported. All tests were two-tailed and the level of significance was set at $\alpha = 0.05$.

As the data regarding salivary cortisol were skewed, non-parametric correlation analyses (Spearman's rho, r_s) between initial (S1) cortisol concentrations and psychopathology indices were used (EDEQ global, DASS-21 total and core AN symptoms). The non-parametric tests, Mann-Whitney U (U) and Wilcoxon Signed Rank (Z) tests were employed to examine whether the first FCT altered salivary cortisol levels for the whole sample and within real/sham rTMS groups respectively.

Using transformed data, the effects of real versus sham rTMS on salivary cortisol over time were evaluated using a mixed ANOVA (group: real/sham rTMS x time: S3, S4, S5) controlling for cortisol levels at S2 as a baseline measure.

Cortisol concentrations have been associated with reduced homeostatic and hedonic hunger in AN (Lawson et al., 2013). Therefore, correlational analyses were conducted for the entire group between cortisol concentrations (S2) and the additional VAS outcomes relating to 'hunger' and 'urge to eat' (see Chapter 3.3) and the liking of food stimuli (see Chapter 3.4) following the first FCT.

Partial eta squared (η^2) are reported for mixed ANOVAs which is automatically computed within SPSS by dividing the sums of squares for the effect of interest by the total sums of squares i.e. $\eta^2 = SS_{\text{between}}/SS_{\text{total}}$ (Levine & Hullett, 2002). Interpretation of the magnitude of η^2 is 0.01-0.06 = small; 0.06-0.14 = medium and > 0.14 ; large. For non-parametric tests, the effect size r was calculated by dividing the Z statistic by the square root of the number within the sample, i.e. r

$= Z/\sqrt{N}$. Interpretation of the magnitude of r is 0.1 = small, 0.3 = medium and 0.5 = large.

Results

The same 49 right-handed, female individuals described above (Chapter 3.3), randomised to real ($n = 21$, restrictive-AN = 13, binge/purge-AN = 8) and sham ($n = 28$, restrictive-AN = 15, binge/purge-AN = 13) were included in the subsequent analyses.

Baseline characteristics

Please see description of baseline demographic and ED characteristics above (Chapter 3.3) and in Table 3.2. Due to missing/invalid data, there were 45 complete (from S1-S5) salivary cortisol data sets (real = 19, sham = 26), which were used in subsequent analyses. The demographic and ED/general psychopathology characteristics of this sub-sample are similar to those reported in Table 3.2: there were no significant group differences at baseline(2), except for on the EDE-Q shape concern subscale [$t(29.83) = -2.28, p = 0.030, d = 0.83$] where the sham group demonstrated significantly greater psychopathology.

Given the skewed nature of the data, median and inter-quartile ranges (*IQR*) of cortisol concentrations within each real/sham group at each collection TP are presented in Figure 3.8. Whilst there was a wide range of values, median scores were around normal ranges for afternoon/evening cortisol concentrations in adult females (< 9.90 nmol/L) and therefore do not suggest hypercortisolemia.

Spearman's rho (r_s) did not indicate any significant associations between initial cortisol concentrations (S1) and psychopathology indices i.e. EDEQ global, DASS-21 total and the composite core AN symptoms.

Salience of food challenge task

There were no significant differences between groups in cortisol concentrations at baseline(2)/S1 [$U = 289, p = 0.920, r = 0.01$]. In the whole sample ($N = 45$), the FCT did not significantly alter salivary cortisol concentrations [$Z = -0.07, p =$

0.942, $r = 0.01$] nor did the FCT significantly alter concentrations within either group: real [$Z = -0.64$, $p = 0.520$, $r = 0.14$], sham [$Z = -0.37$, $p = 0.707$, $r = 0.07$].

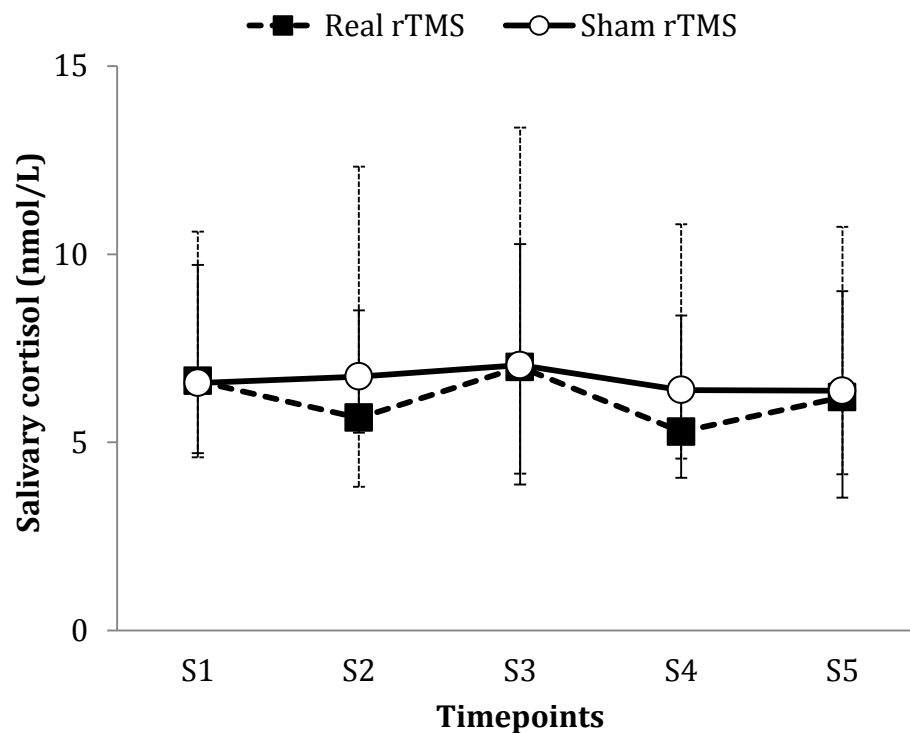


Figure 3.8 Salivary cortisol concentrations for each of the real/sham group. Median ± IQR reported

The median ± IQR of cortisol concentrations (in nmol/L) from S1-S5 in the real (6.63 ± 5.46, 5.65 ± 8.51, 7.00 ± 9.20, 5.28 ± 6.23, 6.20 ± 6.58) and sham (6.58 ± 5.01, 6.75 ± 3.25, 7.05 ± 6.39, 6.39 ± 4.31 and 6.37 ± 5.48) groups respectively.

Outcome

Log transformations were used in mixed ANOVA analyses and controlling for scores at TP2, there were no significant interaction effects [$F(1.54) = 0.50$, $p = 0.561$, $\eta^2 = 0.01$], or effects of time [$F(1.55) = 2.75$, $p = 0.084$, $\eta^2 = 0.06$] or stimulation type [$F(1) = 1.37$, $p = 0.248$, $\eta^2 = 0.03$] on salivary cortisol concentrations. To examine the relationship between cortisol and homeostatic and hedonic appetite, correlations were conducted for the entire sample following the first FCT. Cortisol concentrations (S2) were correlated with the additional VAS relating to ‘hunger’ and ‘urge to eat’ and the food ‘liking’ outcomes (see Chapter 3.3 and 3.4) at TP2. There were no significant correlations across any of these measures.

Discussion

The current findings did not support our hypothesis: compared to sham, real rTMS did not significantly reduce salivary cortisol concentrations. Moreover, salivary cortisol concentrations were not associated with ED/general psychopathology, nor were there any demonstrated relationships between cortisol and homeostatic or hedonic appetite ratings.

The lack of observed changes in salivary cortisol concentrations following rTMS replicates our previous findings in AN (Van den Eynde, Guillaume, et al., 2013). However, our data are not consistent with studies in both healthy individuals (Baeken et al., 2014) and other psychiatric disorders such as depression (Baeken et al., 2009) and BN (Claudino et al., 2011), which have reported reduced salivary cortisol concentrations following HF rTMS to the left DLPFC. One possible explanation is that general salivary cortisol concentrations within this group of individuals with AN were not indicative of hypercortisolemia. Also, whilst HPA axis hyperactivity is well documented in AN, it has been found in weight-restored AN, i.e. it may be trait related (Lo Sauro et al., 2008). Therefore, given its stability throughout different stages of illness, it may be less susceptible to the effects of neuromodulation, particularly only a single-session of rTMS.

The findings of Lawson et al. (2013) regarding cortisol concentrations and reduced homeostatic and hedonic appetite ratings were not replicated in this group of individuals with AN. This may be due to protocol differences such as the method of cortisol collection and analysis (saliva versus serum), and the non-fasted versus fasted/fed state of participants.

Limitations

Given the rTMS methodologies employed, this research is arguably an improvement on existing studies of the effects of rTMS on HPA activity in ED. However, this study is underpowered and in addition, factors such as nicotine and caffeine intake may influence HPA axis activity (Gilbert, Dibb, Plath, & Hiyane, 2000; Hellhammer, Wust, & Kudielka, 2009). Whilst the principle

eligibility criteria of this study aimed to exclude individuals who smoke excessively, the consumption of caffeine and smoking prior to assessment was not monitored. Additionally, whilst all participants were tested in the afternoon, the exact timings of saliva sample collections were not recorded and thus controlled for, unlike in our previous study (Claudino et al., 2011). Finally, as crossover protocols with rTMS are problematic, due to the difficulty in adequate blinding of participants, the between-subject nature of the research is likely to have increased inter-individual variability and thus obscured any potential group differences.

Future directions

Given that stress response systems are predominantly regulated by the right PFC (Cerqueira, Almeida, & Sousa, 2008) and that right-sided hyperactivity has been proposed to be associated with AN (Grunwald et al., 2004; Hecht, 2010; Khedr, El Fetoh, El Bieh, Ali, & Karim, 2014), LF rTMS to the right DLPFC may reduce HPA hyper-activity and therefore it is worth investigating. However, given the negligible effects of rTMS on salivary cortisol concentrations in AN that have been reported so far, other biomarkers, e.g. the effects of rTMS on neurocognitive function in AN (see Chapter 4) or alterations to substrates such as BDNF and monoamine neurotransmitters might be more informative within this patient population.

Summary

The data suggest that in AN, HF rTMS to the left DLPFC does not result in a reduction in HPA activity, i.e. salivary cortisol levels are not reduced following rTMS. Since rTMS did not alter cortisol concentrations, this indicates that the rTMS protocol employed was not experienced as something that is very stressful to individuals with AN. Finally, cortisol concentrations were not associated with reduced homeostatic appetite drive in this group of individuals with AN.

Chapter 3.6 Cortical excitability in anorexia nervosa.

As described previously, the intensity at which rTMS is applied, i.e. the strength of the magnetic field, should be based on levels of cortical excitability. This varies from person to person and therefore rTMS studies typically use MT estimates to quantify cortical excitability and to apply the appropriate 'dose' of rTMS for each individual. Along with being an important safety consideration, as cortical excitability can affect the risk of an rTMS induced seizure (Rossi et al., 2009; Wassermann, 1998), measures such as MT also help to provide an understanding of neurophysiological mechanisms such as intracortical inhibitory and facilitatory networks, and cortico-cortical connectivity (Bunse et al., 2014).

A number of TMS based methodologies can be used to investigate cortical excitability (Table 3.12). Resting and active MT estimations (RMT and AMT), i.e. the excitability of the motor cortex whilst a peripheral muscle is either relaxed or engaged, are commonly used (Rossini et al., 1994) and the amplitude of MEP also provide a measure of cortical excitability (Zaaroor, Pratt, & Starr, 2003). In contrast, the cortical silent period (CSP), defined as the duration between the onset of an MEP and the return to normal electromyography (EMG) activity, is often used to assess levels of cortical inhibition (Bunse et al., 2014; Cantello, Gianelli, Civardi, & Mutani, 1992).

The use of paired-pulse TMS, i.e. applying a conditioning pulse prior to the test pulse, enables alternative measurements of cortical activity. The time of the inter-stimulus interval (ISI) and the magnitude of conditioning/test stimuli can both be varied in paired-pulse TMS designs to examine intracortical facilitation (ICF) or short-interval intracortical facilitation (SICF) (Kujirai et al., 1993; Nakamura, Kitagawa, Kawaguchi, & Tsuji, 1997; Ziemann, 2004) and short- or long-interval intracortical inhibition (SICI/LICI) (Kujirai et al., 1993). Finally, transcallosal inhibition (TCI) involves applying a conditioning TMS pulse to the motor cortex of one hemisphere followed by a test stimulus to the other and enables an assessment of interhemispheric activity (Ferber et al., 1992).

Table 3.12 Techniques used to measure cortical inhibition and excitability.

Measure	Description
<i>Single-pulse TMS</i>	
Motor evoked potential (MEP)	Overall reaction of a peripheral muscle measured by EMG induced via TMS to contralateral motor cortex.
Resting motor threshold (RMT)	Defined as the minimum stimulus required to evoke a minimum of 5 out of 10 MEP > 50 μ V in a relaxed/resting muscle.
Active motor threshold (AMT)	Defined as the minimum stimulus required to evoke a minimum of 5 out of 10 MEP > 50 μ V whilst the target muscle is voluntary contracted.
Cortical silent period (CSP)	Suppression/reduction of muscle activity following TMS to the contralateral motor cortex. It is the time period from onset of MEP and return of EMG activity.
<i>Paired-pulse TMS</i>	
Intracortical facilitation (ICF)	Sub-threshold conditioning stimulus, long (7-20ms) ISI, supra-threshold test stimulus results in cortical excitability.
Short-interval intracortical facilitation (SICF)	Supra-threshold conditioning stimulus, short discrete ISI (1.1-1.5ms, 2.3-2.9ms, 4.1-4.4ms), sub-threshold test stimulus results in cortical facilitation.
Short-interval intracortical inhibition (SICI)	Sub-threshold conditioning stimulus, short (~2-5ms) ISI, supra-threshold test stimulus results in cortical inhibition.
Long-interval intracortical inhibition (LICI)	Supra-threshold conditioning and test stimulus separated by 50-200ms results in cortical inhibition.
Transcallosal inhibition (TCI)	A conditioning stimulus given to motor cortex of one hemisphere and is followed by a second stimulus to the other hemisphere. Used to determine interhemispheric inhibition.

μ V: microvolt, EMG: electromyography; ms: millisecond; ISI: inter-stimulus interval

Whilst the development and use of such techniques has led to improvements in our understanding of neurophysiological processes, it has also identified alterations in cortical inhibition and excitability within neurological and psychiatric disorders. A number of recent systematic reviews and meta-analyses have examined studies that assess cortical activity within psychiatric conditions and have demonstrated ubiquitous inhibitory deficits proposed to result from impairments in GABAergic modulated inhibition (Bunse et al., 2014; Radhu et al., 2013; Radhu, Ravindran, Levinson, & Daskalakis, 2012). Reduced SICI is the most consistent finding across disorders and whilst such general inhibitory deficits have been proposed, Radhu et al. (2013) also suggest that obsessive compulsive disorder, major depression and schizophrenia demonstrate disease-specific alterations in cortical excitability. Moreover, increased RMT, particularly within the left hemisphere, has been demonstrated in depression (Levinson et al., 2010; Maeda, Keenan, & Pascual-Leone, 2000). Whilst these findings are highly relevant and important, a critical confounding factor is that psychiatric patients are commonly on medication, which is known to affect cortical excitability (Ziemann, 2004). Despite this, these, and similar findings in non-medicated patients (Bunse et al., 2014), suggest that measures of cortical excitability may complement existing diagnostic tools. Moreover, such findings may enable more targeted pharmacological and neuromodulatory interventions.

Despite a) evidence for altered cortical excitability across psychiatric disorders, b) the increasing understanding of ED as brain-based problems, and c) the growing number of neuromodulation studies in ED, there is a lack of data on cortical excitability in ED such as AN. While determining MT is a standard procedural requirement of applying rTMS, studies of rTMS in ED to date usually omit data on this parameter (Downar et al., 2012; Hausmann et al., 2004; Kamolz et al., 2008; McClelland, Bozhilova, Nestler, et al., 2013; Van den Eynde et al., 2010; Van den Eynde, Guillaume, et al., 2013; Walpoth et al., 2008). In a recent study, however, by Khedr, El Fetoh, et al. (2014) an examination of cortical excitability in AN was conducted. In this, 14 individuals with AN were matched with HC and cortical excitability was examined via both RMT and AMT,

MEP, CSP, TCI and SICI (see Table 3.13). Compared to controls, individuals with AN demonstrated reductions in RMT in both hemispheres, MEP onset latencies in both left and right motor/esophageal regions and TCI duration. Also, the reduction in RMT and TCI duration were associated with AN (but not depressive) symptoms. Khedr, El Fetoh, et al. (2014) suggest that reductions in GABAergic inhibition along with diffuse hyperexcitability in the relaxed state, is a reflection of AN patients' inability to relax and of their typically anxious temperament. Importantly, a high proportion (77%) of the patients were on medication, which is likely to have influenced the results. Nonetheless, these findings have implications for our understanding of the neural basis of AN and also have safety implications when applying rTMS to this patient population.

Alterations in cortical excitability have been reported across psychiatric conditions and preliminary data suggest that individuals with AN have increased levels of cortical excitability which is positively associated with symptomatology. Whilst the use of rTMS in AN is important in understanding neural mechanisms and exploring novel intervention options, such research also provides a platform to explore cortical activity in ED. This chapter examines and quantifies cortical excitability in AN and we hypothesise that cortical excitability will be associated with AN symptoms.

Methods

Participants

Recruitment and randomisation procedures are described in Chapter 3.2.

Procedures

A description of procedures is provided in Chapter 3.2.

Measures

Baseline

Baseline measures are described in Chapter 3.3.

Cortical excitability

As outlined previously (see Chapter 3.2) a Magstim Rapid device using a real rTMS figure-of-eight coil was used to establish each participants resting (i.e. RMT). EMG recordings from the FDI muscle of the right hand were acquired with surface electrodes placed on the FDI, on the inside of the ipsilateral index finger and a ground electrode placed on the wrist. The left M1 was located on the Brainsight software (by eye, i.e. not using imaging co-ordinates) and participants' MT was defined as the minimum stimulus required to evoke 5 out of 10 MEP greater than 50µV. This procedure was conducted according to the 'lower threshold' method starting at 40% of stimulator output and increasing in increments of 5 until 5 out of 10 responses were greater than 50µV (Rossini et al., 1994; Rothwell et al., 1999). This process was identical across both real/sham groups, that is, all participants' MT were determined using real TMS coils. A **higher RMT estimation indicates reduced cortical excitability**; i.e. reduced cortical excitability requires a higher stimulation output to meet MT requirements.

Statistical analysis

Statistical analyses were performed using IBM® SPSS® software (Version 22). All tests were two-tailed and the level of significance was set at $\alpha = 0.05$.

Descriptive statistics are reported for measures of cortical excitability (RMT) and the subsequent stimulation output parameters used. The data was normally distributed so independent t-tests were employed to examine any differences in MT estimations between AN subtypes (restrictive versus binge/purge), participants who were or were not taking medication and real/sham groups. Pearson's correlation analyses regarding MT and psychopathology indices (i.e. EDEQ, DASS-21) were used.

Cohen's *d* effect sizes are reported for t-tests and were computed by dividing the difference in means by the pooled standard deviation i.e. $d = \frac{M_1 - M_2}{\sqrt{(SD_1^2 + SD_2^2) / 2}}$. Interpretation of the magnitude of Cohen's *d* effect sizes is 0.15-0.40 = small; 0.4-0.75 = medium and > 0.75: large (Cohen, 1988).

Results

The same 49 right-handed, female individuals described in Chapter 3.3, randomised to real ($n = 21$, restrictive-AN = 13, binge/purge-AN = 8) and sham ($n = 28$, restrictive-AN = 15, binge/purge-AN = 13) were included in the subsequent analyses.

Baseline characteristics

Baseline characteristics are described in Chapter 3.3 and presented in Table 3.2.

Cortical excitability

In this group of 49 individuals with AN, measurements of cortical excitability, as indexed by RMT of the left hemisphere and quantified by the output of the Magstim TMS machine, were higher ($M = 55.20$, $SD = 5.92$) than those reported previously ($M = 31.60$, $SD = 4.10$) by Khedr, Elfetoh, et al. (2014). Individuals with a restrictive ($M = 55.11$, $SD = 5.53$) or binge/purge ($M = 55.33$, $SD = 6.54$) AN diagnosis did not differ on measures of RMT [$t(47) = -0.13$, $p = 0.896$, $d = 0.04$]. Additionally, there were no significant differences between measurements of RMT in those who were ($n = 34/49$: 69%, $M = 54.94$, $SD = 5.80$) or were not ($n = 15/49$: 31%, $M = 55.80$, $SD = 6.34$) taking medication [$t(47) = -0.46$, $p = 0.645$, $d = 0.13$]. Finally, there were no significant differences between real/sham groups on RMT estimations [$t(47) = -0.89$, $p = 0.378$, $d = 0.26$]; (real $M = 54.33$, $SD = 4.98$; sham $M = 55.86$, $SD = 6.55$), or the intensity of rTMS output used [$t(47) = -0.48$, $p = 0.636$, $d = 0.14$]; (real $M = 59.86$, $SD = 5.43$; sham $M = 60.74$, $SD = 7.75$).

There was a trend towards an inverse relationship between RMT and BMI [$r = -0.24$, $p = 0.094$], indicating that increased RMT (i.e. reduced cortical excitability) is associated with lower BMI. In line with this finding is the trend for a positive correlation between RMT and EDE-Q global score [$r = 0.27$, $p = 0.062$], in addition to RMT and EDE-Q restraint [$r = 0.26$, $p = 0.066$] and eating concern [$r = 0.26$, $p = 0.075$] subscale scores. These findings indicate moderate associations between reduced cortical excitability and worse ED

symptomatology. However, there were no significant correlations between RMT and EDE-Q weight [$r = 0.22, p = 0.134$] or shape [$r = 0.21, p = 0.155$] subscales. Similarly, there were no significant correlations between RMT and DASS-21 total score [$r = 0.14, p = 0.339$] or depression [$r = 0.14, p = 0.327$], anxiety [$r = 0.14, p = 0.338$] and stress [$r = 0.07, p = 0.610$] subscale scores.

Discussion

The estimations of cortical excitability, i.e. RMT, reported here were higher than we expected. The type of AN diagnosis (restrictive or binge/purge) or whether or not individuals were on medication did not affect measures of cortical excitability. Interestingly, there was a trend towards RMT being inversely correlated with BMI and positively associated with other measures of ED symptomatology. In other words, reduced cortical excitability was moderately associated with lower weight and worse ED symptoms. However, this was not accompanied by relationships between cortical excitability and measures of general psychopathology (e.g. mood).

GABAergic, dopaminergic and glutamatergic mechanisms have been implicated in cortical inhibitory and facilitatory networks and are likely to underlie alterations in cortical excitability that have been reported in AN (Maeda et al., 2000). Moreover, whilst some data supports the notion of right-sided prefrontal hyperexcitability in AN (Grunwald et al., 2004; Hecht, 2010; Seeger et al., 2002; Uher et al., 2003), the present findings of increased RMT and thus reduced cortical excitability of the left motor cortex suggest that this could be associated with opposing hypoactivity in the ipsilateral left hemisphere.

The present data are not consistent with the literature regarding cortical excitability in AN, albeit only one study. The RMT estimates were higher than those reported previously in AN, and we found that reduced (rather than increased) cortical excitability was moderately associated with worse symptomatology. In contrast, Khedr, Elfetoh, et al. (2014) found that individuals with AN demonstrated increased motor cortical excitability (i.e. lower RMT) compared to controls and this was associated with ED symptoms. However, an increased RMT and thus reduced motor cortical excitability is a consistent

finding across other studies of psychiatric conditions, particularly depression (Bunse et al., 2014). Moreover, in individuals with major depressive disorder, inter-hemispheric differences in MT have been demonstrated (left > right) and show reduced excitability of the left hemisphere (Maeda et al., 2000). Additionally, reduced excitability of the frontal cortex differentiates treatment-resistant depressed patients from non-medicated, euthymic medicated patients and HC (Levinson et al., 2010).

There are substantial differences between our study and that of Khedr, El Fetoh, et al. (2014). Our study group was almost four times the size of Khedr, El Fetoh, et al. (2014) and due to our narrow inclusion criteria our sample was older and had a higher average BMI and these are factors that may influence cortical excitability (Bashir et al., 2014). Moreover, whilst Khedr, El Fetoh, et al. (2014) did not mention the illness duration of participants, the mean duration of illness in our sample was greater than 10 years. Therefore, the treatment-resistant nature of our participants and their reduced cortical excitability might reflect the similar findings reported in treatment-resistant depression (Levinson et al., 2010). In this context, it is noted that 45% of our participants had a co-morbid diagnosis of depression, whilst none of the Khedr, El Fetoh, et al. (2014) group had other clinically relevant disorders. ED symptoms were also assessed differently (EDE-Q versus EDI/EAT), and although comparable (69% versus 77%), more of the Khedr, El Fetoh, et al. (2014) participants were medicated.

A number of procedural differences are also of note. Khedr, El Fetoh, et al. (2014) used six measures of cortical excitability and we only used one. Whilst more measurements provide a better overall assessment of cortical activity, the accumulative effects of TMS on neural activity influences cortical excitability, at least in the short term. Similarly, the accuracy of MT estimations is dependent on the type of equipment used, e.g. TMS machine and electrodes, the environment in which participants are tested in, e.g. temperature, and the consumption/use of substances such as caffeine, alcohol and nicotine, prior to assessment. Finally, given that our protocol was primarily designed to assess the effects of rTMS on core AN symptoms, our participants were exposed to a food cue exposure task prior to MT estimations and, whilst the effects of this

task weren't significantly salient (see Chapter 3.3), its use may have influenced our results regarding cortical excitability.

Limitations

Whilst this is the first rTMS study to report MT and stimulation outputs used in ED patients, it lacks a healthy control comparison group, which is unfortunate. Since measures of MT were collected primarily for the application of rTMS, unlike Khedr, El Fetoh, et al. (2014), we did not assess any other measurements of cortical excitability and this is a further limitation. In addition, medication affects cortical excitability and over half of our participants were on medication. Finally, this study measures activity in the motor cortex, when the condition of interest, AN, is related to non-motor processes.

Future directions

Future studies involving rTMS in ED should report and consider cortical excitability. Moreover, cortical excitability of areas other than the motor cortex, i.e. those implicated in neural models of ED and targeted with neuromodulation, such as the DLPFC, should be determined using combined EEG/TMS protocols. Furthermore, the association between cortical excitability and symptoms of AN requires further clarification, as it may be a viable diagnostic tool and/or enable targeted neuromodulatory interventions.

Summary

This study describes and discusses the issues related to cortical excitability in AN and more widely, within neuromodulation research in ED. In this group of individuals with AN, there were trends demonstrating associations between reduced cortical excitability, lower BMI and worse AN symptomatology.

Chapter 3.7 Cardiac safety, tolerability and acceptability of repetitive transcranial magnetic stimulation in anorexia nervosa

Whilst rTMS has proven to be a safe and tolerable technique in healthy individuals and patients with psychiatric and neurological disorders (Loo et al., 2008), safety considerations remain important. The most severe side effect reported following rTMS, although relatively rare, is the induction of a seizure, however, other adverse events such as syncope and transient pain (e.g. headaches) have also been reported (Rossi et al., 2009). It is therefore important to use caution when delivering rTMS in patient populations that have never, or only in a preliminary fashion, been investigated with rTMS.

The use of neuromodulation techniques such as rTMS in ED patients is relatively novel; research is limited to a few RCT in BN (Van den Eynde et al., 2010; Walpoth et al., 2008) and a number of case reports/studies in both BN (Downar et al., 2012; Hausmann et al., 2004) and AN (Kamolz et al., 2008; Khedr, Elfetoh, et al., 2014; McClelland, Bozhilova, Nestler, et al., 2013). Thus, there is a need to further investigate the suitability of rTMS in this patient population.

ED have been associated with cardiovascular complications, including bradycardia, hypotension, cardiac arrhythmias and cardiac arrest (Casiero & Frishman, 2006; de Simone et al., 1994; Kollai, Bonyhay, Jokkel, & Szonyi, 1994). Non-invasive neuromodulation such as rTMS may be capable of modulating cardiovascular function (Cogiamanian et al., 2010; Sampaio, Fraguas, Lotufo, Bensenor, & Brunoni, 2012). Specifically, a reduction of blood pressure (BP) and heart rate was demonstrated following 10Hz rTMS (Hong et al., 2002) in rats, parasympathetic activity was activated following LF rTMS in healthy humans (Gulli et al., 2013) and modulation of heart rate variability has been shown following two weeks of rTMS treatment in major depression (Udupa et al., 2007). The cardiac safety of rTMS in BN has been established (Van den Eynde et al., 2011) along with preliminary, pilot data on AN (Van den Eynde, Guillaume, et al., 2013): however, there is a need to examine and establish the cardiac safety of rTMS in AN, in larger controlled studies especially given the long-

standing physical debilitation present in AN (Wentz, Gillberg, Gillberg, & Rastam, 2000).

Additionally, starvation has detrimental effects on the development, structure and long-term functioning of the brain (Levitsky & Strupp, 1995; Winick, 1969). Systematic reviews on structural neuroimaging in AN consistently report reductions in brain volume, specifically reduced grey and white matter (Fonville, Giampietro, Williams, Simmons, & Tchanturia, 2014; Van den Eynde, Suda, et al., 2012). Whilst there is some evidence that the neural effects of rTMS are different in atrophic (compared to healthy) brains (Wagner, Eden, et al., 2008), whether or not brain atrophy, and associated reductions in adipose tissue affects the tolerability of rTMS remains unclear.

Finally, since the use of neuromodulation techniques in the treatment of ED is relatively new, it is important to establish patients' attitudes to this type of brain-directed intervention and whether or not they would consider it as a treatment adjunct. Therefore, this chapter examines the cardiac safety, tolerability and acceptability of rTMS as a treatment for AN. It is hypothesised that in individuals with AN, real rTMS will not induce effects on cardiac safety measures (namely BP and pulse) and will be well tolerated (i.e. without severe side effects). It is hypothesised that real rTMS will be reported as more uncomfortable than sham. However, we hypothesise that, if rTMS proves efficacious in AN, affected individuals will consider it as a viable treatment option.

Methods

Participants

Recruitment and randomisation procedures are described in Chapter 3.2.

Procedures

A description of procedures is provided in Chapter 3.2.

Measures

Baseline

Baseline measures are described in Chapter 3.3.

Safety

Cardiac safety was assessed by recording BP (mmHg) and heart rate (beats per minute). This was measured with an A&D Medical UA-767 Plus Digital Blood Pressure Monitor at baseline(2), following MT, following the real/sham rTMS session and at the end of the testing session. Participants sat upright for this and it was done on the same arm for each participant.

Tolerability

Participants rated their level of discomfort of the real/sham rTMS immediately after the session. This was done using a 10cm VAS ranging from 0 ‘not painful at all’ to 10 ‘extremely painful’.

At the end of the testing sessions, to assess any adverse effects or pain associated with the rTMS, participants were asked if they encountered any abnormal experiences, pain or discomfort. This was established by answering yes/no to questions relating to headache, nausea, dizziness/faintness or any discomfort at the site of stimulation or surrounding areas. These side effects were reassessed during the 24 hour follow-up phone call, together with whether or not they took pain killers following the session.

Acceptability

To gauge participants’ attitudes towards rTMS as a treatment for AN, during the 24 hour follow-up phone call, they were asked to answer yes/no to the question: ‘If there is evidence that rTMS reduces some of the symptoms related to anorexia, would it be something you would consider having as a treatment, e.g. each day of the week for four weeks?’

Statistical analyses

Statistical analyses were performed using IBM® SPSS® software (Version 22). Following consultation with a statistician, when normality or other ANOVA assumptions such as homogeneity of variance were violated (assessed via Kolmogorov-Smirnov and Levene's test statistics respectively) log transformations or other non-parametric alternatives were employed. When Mauchly's test of sphericity was violated, Greenhouse-Geisser corrections are reported. All tests were two-tailed and the level of significance was set at $\alpha = 0.05$.

The data regarding BP and pulse were normally distributed. The effects of real versus sham rTMS on BP and pulse were evaluated using mixed ANOVAs (group: real/sham rTMS x time: post-MT, post-rTMS, TP4) controlling for BP/pulse at baseline-2/TP1. Independent t-tests were used to compare discomfort ratings of real and sham rTMS. Pearson's chi-square (χ^2) was used to assess the proportion of people reporting physical complaints and having to take painkillers after either real/sham rTMS.

Partial eta squared (η^2) and Cohen's d effect sizes are reported for mixed ANOVAs and independent sample t-tests respectively. Partial eta squared is automatically computed within SPSS by dividing the sums of squares for the effect of interest by the total sums of squares i.e. $\eta^2 = SS_{between}/SS_{total}$ (Levine & Hullett, 2002). Cohen's d was computed by dividing the difference in means by the pooled standard deviation i.e. $d = (M_1 - M_2)/\sqrt{(SD_1^2 + SD_2^2)/2}$. Interpretation of the magnitude of η^2 is 0.01-0.06 = small; 0.06-0.14 = medium and > 0.14; large; and for Cohen's d effect sizes 0.15-0.40 = small; 0.4-0.75 = medium and > 0.75: large (Cohen, 1988).

Results

The same 49 right-handed, female individuals described above (Chapter 3.3), randomised to real ($n = 21$, restrictive-AN = 13, binge/purge-AN = 8) and sham ($n = 28$, restrictive-AN = 15, binge/purge-AN = 13) were included in the subsequent analyses.

Baseline information

Baseline demographic and ED characteristics are described in Chapter 3.3 and presented in Table 3.2.

Safety

One participant was missing complete BP/pulse data and therefore, 48 participants were included in analyses of cardiac safety (real = 21, sham = 27). Controlling for baseline (2), there were no significant interaction, time or group effects on BP or pulse (see Table 3.13).

Table 3.13 Mixed ANOVA results of blood pressure and pulse following real/sham rTMS. Mean \pm SD reported.

	Time point	Real rTMS (<i>n</i> = 21)	Sham rTMS (<i>n</i> = 27)	ANOVA Time	ANOVA Group	ANOVA Interaction Group x Time
Systolic blood pressure (mmHg)	Post MT	102.14 \pm 8.84	102.07 \pm 9.59	<i>F</i> (1.76) = 0.73 <i>p</i> = 0.470 η^2 = 0.02	<i>F</i> (1) = 0.03 <i>p</i> = 0.857 η^2 = 0.00	<i>F</i> (1.76) = 1.94 <i>p</i> = 0.155 η^2 = 0.04
	Post rTMS (TP3)	100.62 \pm 13.83	103.56 \pm 10.70			
	End of session (TP4)	106.76 \pm 8.98	104.19 \pm 13.92			
Diastolic blood pressure (mmHg)	Post MT	66.85 \pm 8.54	67.89 \pm 8.00	<i>F</i> (2) = 0.01 <i>p</i> = 0.993 η^2 = 0.00	<i>F</i> (1) = 1.13 <i>p</i> = 0.294 η^2 = 0.02	<i>F</i> (2) = 0.87 <i>p</i> = 0.424 η^2 = 0.02
	Post rTMS (TP3)	67.33 \pm 9.29	67.52 \pm 8.91			
	End of session (TP4)	70.67 \pm 8.57	69.44 \pm 9.29			
Pulse (beats per minute)	Post MT	67.95 \pm 14.95	70.30 \pm 11.19	<i>F</i> (2) = 1.75 <i>p</i> = 0.180 η^2 = 0.04	<i>F</i> (1) = 1.22 <i>p</i> = 0.275 η^2 = 0.03	<i>F</i> (2) = 0.50 <i>p</i> = 0.606 η^2 = 0.01
	Post rTMS (TP3)	66.24 \pm 13.10	70.15 \pm 11.67			
	End of session (TP4)	69.86 \pm 13.13	71.52 \pm 12.66			

Tolerability

As stated previously, 2 of the 23 participants randomised to receive real rTMS withdrew after the first few trains of stimulation due to discomfort. These two participants described rTMS as unbearably uncomfortable and felt that they could not sit through all of the 20 rTMS trains. Of the 49 remaining individuals, those who had real rTMS found it significantly more uncomfortable than those who had sham [$t(46) = 6.33, p < 0.001, d = 1.87$] (see Figure 3.9).

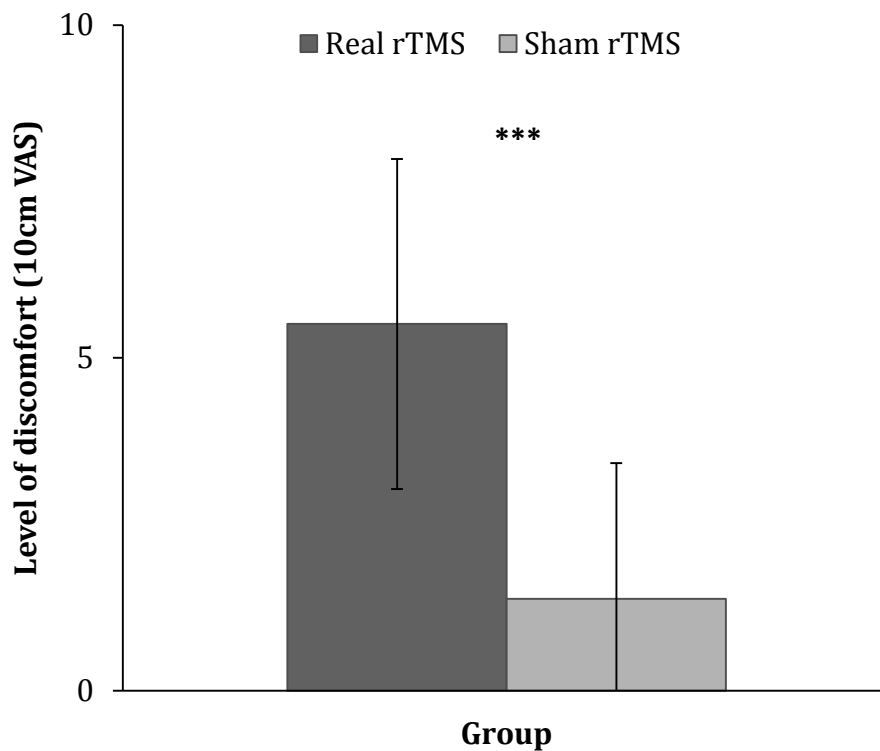


Figure 3.9 Level of discomfort reported following real/sham rTMS. Mean \pm SD reported.

**** $p < .001$. Scores relate to a 10cm visual analogue scale and therefore range from 0 (no discomfort) to 10 (extreme discomfort). The mean \pm SD values are real: 5.51 ± 1.38 , sham: 1.38 ± 2.04 .*

There were no significant differences between real/sham groups in the number of physical complaints (typically feeling dizzy/dazed or having a headache) reported [$\chi^2(1) = 0.73; p = 0.394, N = 49$] (5/21 real; 4/28 sham) or whether or not participants had to take painkillers [$\chi^2(1) = 0.44; p = 0.505, N = 49$] (2/21 real, 1/28 sham).

Acceptability

When considering having rTMS as a treatment, 83% (19/23) of people who had real rTMS and 93% (26/28) who had sham, said they would be interested in rTMS as a therapeutic intervention for AN.

Discussion

In line with our hypotheses, rTMS proved to be a safe, well tolerated and an acceptable potential therapeutic technique for AN. Measures of cardiac safety, BP and pulse, remained unchanged following both real and sham rTMS. Whilst real rTMS was reported to be more uncomfortable than sham, no severe side effects were reported, nor were there any differences in the reported physical complaints or pain-killers taken following real/sham rTMS. Finally, over 80% of people that had real rTMS would consider it as a treatment.

The current findings are in accord with previous data suggesting cardiac safety and tolerability of rTMS in both AN (Van den Eynde, Guillaume, et al., 2013), BN (Van den Eynde et al., 2011) and other groups (Gulli et al., 2013; Pecuch, Evers, Folkerts, Michael, & Arolt, 2000). Moreover, the BP and pulse measures in the present group are within normal ranges and therefore do not suggest hyper/hypotension. These are the first data in AN to compare safety and tolerability outcomes of real to sham rTMS, and suggest that real rTMS is significantly more uncomfortable than sham for people with AN. This has implications for study design aspects such as the limited practicality of crossover rTMS designs and for ensuring adequate blinding. Importantly, rTMS was seen as a feasible potential treatment for AN, as demonstrated by the high proportion of people who would consider having it on a daily basis for four weeks.

Limitations

Cardiac safety of rTMS in AN was established via BP and pulse measurements but other safety measures are worth considering. For example, given brain atrophy in AN (Fonville et al., 2014) and preliminary evidence for increased

cortical excitability (Khedr, El Fetoh, et al., 2014), concurrent EEG would enable direct physiological monitoring of neural excitability and the ability to pre-empt any increased risk of seizure (Rossi et al., 2009; Wassermann, 1998). Whilst over 90% of people who had sham rTMS said they would consider it as a treatment, they had not actually experienced real rTMS and given the differences in discomfort reported between real/sham rTMS, fewer participants in the sham group might actually consider having it in a longer-term, therapeutic manner. Furthermore, the minimum BMI (14) and general medical stability required to participate in the current study, limits the generalisation of these findings regarding safety and tolerability to severely low weight individuals.

Future directions

The results of this study have implications for future neuromodulation research in AN. Since this application of HF rTMS was safe, relatively well tolerated and accepted in AN, more uncomfortable techniques that are arguably more focal/effective, such as theta-burst stimulation (TBS), may also be reasonable procedures for these patients. In addition, whilst individuals with AN would consider rTMS as a treatment, the use of neuromodulation techniques for the treatment of ED may not be widely favoured by clinicians. Since clinicians are patients' primary point of contact, it will be important to examine clinicians' views towards these types of adjunctive neuromodulatory therapies in ED.

Summary

In this group of individuals with AN rTMS proved to be safe and well tolerated, although more uncomfortable than sham rTMS. A large proportion of individuals with AN would consider having it as a treatment.

Chapter 3.8 Overall Summary

The findings reported in this group of 51 female individuals, with relatively severe AN, supported our primary hypothesis; compared to sham, reduced core AN symptoms were reported following real rTMS (Chapter 3.3). Importantly, among participants, the concealment of intervention allocation was partially successful. The liking of sweet, shortbread biscuits was significantly increased following real rTMS, but reduced following sham (Chapter 3.4). Salivary cortisol concentrations were unchanged following rTMS, suggesting that rTMS does not down-regulate HPA axis activity in AN and also that the procedure is not overly stressful (Chapter 3.5). Reduced cortical excitability was moderately associated with AN symptoms (Chapter 3.6). Finally, rTMS proved to be a safe, tolerable and acceptable intervention within this patient population (Chapter 3.7).

The research reported here is in partial agreement with existing literature. Whether or not rTMS temporarily alters AN symptoms significantly more than placebo responses, remains unclear as does the neurobiological mechanisms underlying its action. Whilst interpretation of the research reported in this chapter is limited by a lack of power, it is an improvement on existing studies of rTMS in ED, because it uses improved methodologies.

Preliminary evidence exists for the beneficial effects of neuromodulation in AN when delivered in a repeated, therapeutic manner yet limited behavioural and physiological findings following a single-session of rTMS have been found in other psychiatric disorders. Future controlled trials, with multiple rTMS session protocols, may be more informative and appropriate if wanting to extrapolate findings to potential longer-term therapeutic effects and considering rTMS as an adjunctive treatment for AN. Moreover, given the lack of physiological effects reported here, investigating neurocognitive effects and employing neuroimaging modalities alongside rTMS may provide the best opportunity in exploring disease mechanisms and biomarkers of response to neuromodulation in AN.

Chapter 4. The effects of repetitive transcranial magnetic stimulation on temporal discounting in anorexia nervosa

Introduction

The concept of delayed gratification, that is, the ability to resist immediate temptations in favour of a delayed reward, was first explored in the well-known Stanford marshmallow experiment (Mischel, Ebbesen, & Zeiss, 1972). In this study, children were told that if they resisted eating a marshmallow that was placed in front of them whilst the researcher was out of the room, they could have two marshmallows when the researcher returned. The ability to delay gratification, i.e. wait until the researcher returned in order to gain the larger reward, has been investigated in follow-up studies of these same children and is associated with academic and personal success in later life (Mischel, Shoda, & Rodriguez, 1989; Shoda, Mischel, & Peake, 1990) and a lower BMI up to three decades later (Schlam, Wilson, Shoda, Mischel, & Ayduk, 2013). Similarly, childhood self-control predicts physical health, substance dependence, personal finances and criminal outcomes, independent of intelligence and social class (Moffitt et al., 2011). Given these and other findings, the ability (or inability) to delay gratification is a widely pertinent construct and proposed to be a relatively stable personality trait (Kirby, 2009; Odum, 2011).

Studies such as the ‘marshmallow test’ resemble everyday decisions involving conflict between pleasure seeking, impulsive drives and deliberate, prudent motivations. Extensive research in humans has examined such decision making paradigms and demonstrates that a delayed, or less probable reward is not as valuable as an immediately available reward (Cardinal, 2006). Based on the observation that the subjective value of a delayed reward decreases as a function of its temporal delay (Green, Myerson, & Ostaszewski, 1999), the **rate at which a future reward is devalued is referred to as ‘delay discounting (DD)’ or ‘temporal discounting (TD)’**.⁴

Rates of discounting vary between individuals and intertemporal choice tasks are used to capture discounting behaviours. Typically, TD tasks involve a

⁴ For the purpose of consistency the term temporal discounting (TD) is used throughout, despite the fact that the literature discussed uses both terms. TD and DD are conceptually identical and therefore the terms are interchangeable.

number of binary choices, requiring participants to choose between monetary or consumable (e.g. food) rewards that are available immediately (smaller-sooner; SS), and a reward of larger magnitude that is available after a variety of delay periods (larger-later; LL) (Estle, Green, Myerson, & Holt, 2007; Odum & Rainaud, 2003). For each delay period assessed, the point of subjective equality i.e. when the LL reward is deemed equal to the SS reward is termed the **indifference point (IP)**. Using each of the IP of a number of different delay periods, a general measure of discounting can be estimated in two ways. A hyperbolic function can be fitted to the indifference points for each delay and k , a constant that characterises an individual's rate of discounting is used to typify TD (Richards et al., 1999). The value of k can range from 0 to 1 and participants with **larger k values (i.e. steeper slope of discounting) show greater TD** and more choice impulsivity. Alternatively, area under the curve (AUC) measurements provide theoretically neutral accounts of TD (Myerson, Green, & Warusawitharana, 2001). The AUC is generated by calculating the area under the empirical discounting function, i.e. summing the trapezoid of each IP and also has a value between 0 and 1. However, **smaller AUC values represent greater rates of discounting** and thus more choice impulsivity (see Figure 4.1 and the methods section for further details).

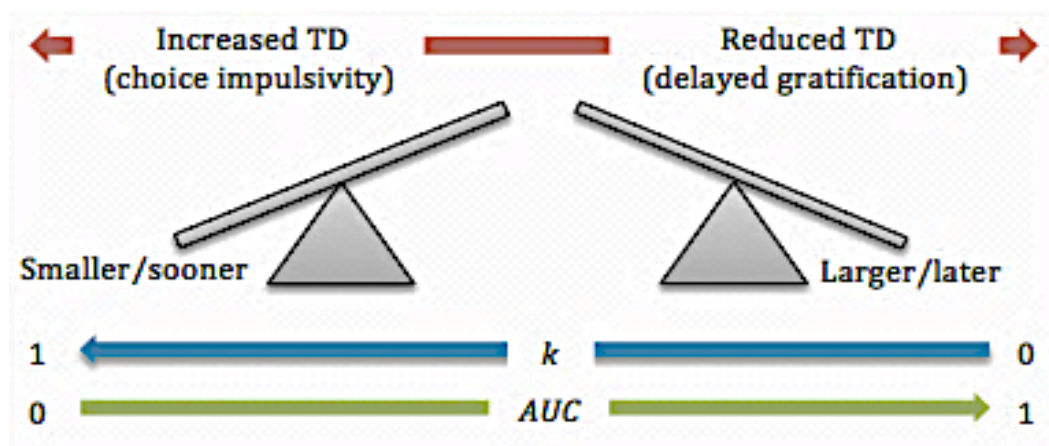


Figure 4.1 Schematic representation of temporal discounting and its measurement

k is a constant within a hyperbolic function that represents an individual's rate of discounting; larger k values indicate increased temporal discounting (TD). Area under the curve (AUC) is a theoretically neutral measure of TD; reduced AUC indicates increased TD.

Behavioural TD tasks are thought to measure different and implicit components of decision making that are not otherwise captured through self-report inventories (Reynolds, Ortengren, Richards, & de Wit, 2006). Many studies have used TD tasks with both monetary and disorder-specific related rewards to examine altered motivational behaviours that are relevant to a wide range of disorders. For example, individuals with conduct disorder (White et al., 2014), autism (Chantiluke et al., 2014), attention-deficit/hyperactivity-disorder (Demurie, Roeyers, Baeyens, & Sonuga-Barke, 2012), major depression (Pulcu et al., 2014) and schizophrenia (Heerey, Robinson, McMahon, & Gold, 2007) demonstrate increased rates of TD and are argued to be more impulsive than their healthy counterparts. Similarly, increased discounting of future monetary and disorder-specific rewards (e.g. cigarettes and food) has been demonstrated in relation to unhealthy behaviours such as smoking and disordered eating (for reviews see Reynolds, 2006; Story, Vlaev, Seymour, Darzi, & Dolan, 2014). These findings are likely to represent the conflict between immediate temptations (e.g. cigarettes/alcohol/food) and the pursuit of long-term goals/rewards (e.g. health/sobriety/weight management). Therefore, TD tasks are useful in exploring the construct of choice impulsivity and delayed gratification mechanisms within a wide range of disorders.

Temporal discounting and disordered eating

Choice impulsivity is highly pertinent in relation to eating behaviour. For example, impaired inhibitory control has been associated with overeating and BMI (Jasinska et al., 2012) whilst lower levels of impulsivity are associated with dietary success and restraint (van Koningsbruggen, Stroebe, & Aarts, 2013). A number of studies to date have therefore investigated TD behaviours in relation to disordered eating (see Table 4.1). Initially, studies suggested no difference in rates of TD between obese and healthy weight females (Nederkoorn, Smulders, Havermans, Roefs, & Jansen, 2006), however others have reported that obese women (but not men) demonstrate increased TD (Weller, Cook, Avsar, & Cox, 2008). Similar findings have also been found in both adolescents (Fields, Sabet, & Reynolds, 2013) and clinical, BED samples (Davis, Patte, Curtis, & Reid, 2010; Manwaring, Green, Myerson, Strube, & Wilfley, 2011; Mole et al., 2014).

However, differences in levels of education have been shown to account for these differences (Davis et al., 2010), and whilst obese and BED groups demonstrate increased TD compared to controls, differences in TD between individuals who had BED and were obese remain unclear.

More specifically, increased TD (i.e. increased choice impulsivity) has been associated with both food reward sensitivity and food intake in people with obesity (Appelhans et al., 2011). Three recent studies have examined associations between neural activity and discounting behaviours in obesity. During difficult TD choices (i.e. increased deviation from the point of subjective equality of SS/LL rewards) reduced activation in brain areas associated with executive functions is shown to predict weight gain (Kishinevsky et al., 2012). Similarly, reduced neural activity in similar regions during difficult choices was associated with increased TD/impulsive choices (Stoeckel, Murdaugh, Cox, Cook, & Weller, 2013). Moreover, reduced TD (and thus a better ability to delay gratification) predicted subsequent weight loss/dietary success and this was associated with increased activity and stronger functional connectivity in the ventromedial PFC (VMPFC) and DLPFC (Weygandt et al., 2013).

Other studies have examined TD behaviour in relation to additional ED related concepts. Leitch, Morgan, and Yeomans (2013) reported no differences in performance on a TD task in women who scored higher (rather than lower) on a measure of uncontrolled eating, despite increased scores on other relevant measures such as the Barrett Impulsivity Scale. In contrast, within a group of heavy drinkers, reduced TD and the ability to delay gratification, predicted dietary restraint, weight and shape concerns (Stojek, Fischer, Murphy, & MacKillop, 2014). However, whilst findings in female college students suggest that reduced TD predicts lower body esteem (Lilienthal & Weatherly, 2013b), choice impulsivity (less TD of a monetary loss) was shown to predict risk for AN (Lilienthal & Weatherly, 2013a). This latter finding is somewhat inconsistent with the only data regarding TD in AN (Steinglass et al., 2012). Compared to controls, individuals with AN show reduced rates of the discounting of future, monetary rewards in a TD task, indicating an enhanced ability to delay gratification. Moreover, TD was particularly reduced in the restrictive AN

subtype. This suggests that reduced TD, rather than increased choice impulsivity, is also associated with psychiatric psychopathology. Specifically, reduced TD behaviours may underlie the extreme self-control over food that facilitates pathological dietary restraint in AN.

In summary, the data so far suggests that increased discounting of future rewards exists in over-eating disorders such as obesity and BED. However, the difference between these two groups is unclear, as are the effects of gender and education levels/intelligence on discounting behaviours. Currently, there are little to no data regarding TD in other ED. Whilst choice impulsivity has been associated with risk of AN, the ability to delay gratification has been associated with dietary restraint, ED related concerns and AN.

Table 4.1 Studies investigating temporal discounting in relation to disordered eating

	N	Sample	Task	Outcome	Findings
<i>Obesity and binge eating disorder</i>					
Nederkoorn et al (2006)	59	Obese ($n=31$) & control ($n=28$) women	Monetary TD task Immediate amount variable, delayed amount fixed (€1k)	k value	No differences on TD found.
Weller et al (2008)	95	Obese men ($n=19$) & women ($n=29$) & HC men ($n=21$) & women ($n=26$)	2 monetary TD tasks (high \$50k & low \$1k) Immediate amount variable, delayed amount fixed (£50k or £1k)	AUC	Obese women showed greater TD than HC. Obese & HC men did not differ
Davis et al (2010)	209	Obese women with BED ($n=65$), obese women without BED ($n=73$) & HC women ($n=71$)	Monetary TD task Immediate amount variable, delayed amount fixed (£100)	Slope of indifference points (k value)	BED & obese women displayed greater TD compared to HC but BED and obese groups did not differ on TD from each other. When group differences in education were accounted for, findings no longer significant.
Appelhans et al (2011)	62	Overweight & obese women	Monetary TD task Immediate amount variable, delayed amount fixed (£100)	AUC	Greater food reward sensitivity was associated with increased palatable food intake only amongst those with increased TD/poor inhibitory control
Manwaring et al (2011)	90	Obese women with BED ($n=30$), obese women without BED ($n=30$) & HC women ($n=30$)	TD with different rewards (money, food, sedentary activity, massage time) Immediate amount variable, delayed amount fixed.	AUC/median subjective values	BED group discount future rewards more steeply than the obese and control groups irrespective of the type of reward offered
Kishinevsky et al (2012)	24	Obese women	Monetary TD task + fMRI Both immediate & delayed choices were variable	Implied k value	Greater activation during difficult TD trials in areas including prefrontal cortex. Less activation on difficult TD trials predicted greater weight gain.
Fields et al (2013)	61	Obese ($n=21$), overweight ($n=20$) & HC adolescents ($n=20$)	Monetary TD task	AUC	Obese & overweight adolescents more impulsive on TD task. No difference between obese & overweight adolescents on TD

HC: healthy controls; BED: binge eating disorder; TD: temporal discounting; k values represent an individual's rate of discounting and $> k$ values indicated greater TD; AUC: area under the curve is a theoretically neutral measure of discounting and $< AUC$ indicates greater TD.

Table 4.1 (continued) Studies investigating temporal discounting in relation to disordered eating.

	N	Sample	Task	Outcome	Findings
Stoeckel et al (2013)	24	Obese women	Monetary TD task + fMRI Immediate choice fixed, later variable	Implied <i>k</i> value	Greater TD correlated with less modulation of activation in executive function regions in response to difficult (compared to easy) TD trials.
Weygandt et al (2013)	16	Obese men (<i>n</i> =3) and women (<i>n</i> =13)	Food-specific delay gratification paradigm + fMRI	<i>k</i> value	Impulse control predicted weight loss. Brain activity in VMPFC & DLPFC correlated with weight loss & stronger functional connectivity associated with dietary success & impulse control
Mole et al (2014)	90	Obese with BED (<i>n</i> =30), obese without BED (<i>n</i> =30) and abstinent alcohol-dependent (<i>n</i> =30) & HC (<i>n</i> =30)	Monetary choice questionnaire	<i>k</i> value	All three groups greater TD than HC.
<i>Disordered eating/other ED related constructs</i>					
Leitch et al (2013)	80	Women with uncontrolled eating/ dietary restraint	Monetary TD task Immediate choice variable, delayed fixed.	AUC	No significant differences across TD task between groups
Stojek et al (2014)	108	Heavy-drinkers	Monetary choice questionnaire (Kirby, 1999)	<i>k</i> value	Lower TD predicted dietary restraint, weight & shape concerns
Lilienthal et al (2013)	146	Female college students	Monetary gain/loss TD task	AUC	Less TD of a delayed monetary loss (impulsive decision) significantly predicted risk for AN
Lilienthal et al (2013)	139	Female college students	Discounting task re: gain/lose weight or improve/worsen complexion. Percentage of lifestyle (0-100%) willing to alter in order to obtain outcome	AUC	Lower impulsivity predicted lower body esteem levels.

HC: healthy controls; BED: binge eating disorder; TD: temporal discounting; fMRI: functional magnetic resonance imaging; k values represent an individual's rate of discounting and > k values indicated greater TD; AUC: area under the curve is a theoretically neutral measure of discounting and < AUC indicates greater TD. VMPFC: ventromedial prefrontal cortex; DLPFC: dorsolateral prefrontal cortex.

Table 4.1 (continued) Studies investigating temporal discounting in relation to disordered eating.

	N	Sample	Task	Outcome	Findings
Anorexia nervosa					
Steinglass et al (2012)	64	Underweight AN (n=36) & HC (n=28)	Monetary TD task Accelerate set; immediate variable, delayed fixed (\$80) & Delay set; immediate fixed (\$45), delayed variable. 3 month time frame	Separate discount factor for accelerate/delay set; similar to AUC	Individuals with AN showed less TD than HC, in particular the restrictive AN subtype. Framing of choices as accelerate/delay affected discount factor; individuals discount future more asked to delay rather than accelerate receipt of reward.

HC: healthy controls; AN: anorexia nervosa; k values represent an individual's rate of discounting and > k values indicated greater TD; AUC: area under the curve is a theoretically neutral measure of discounting and < AUC indicates greater TD.

Neural correlates of temporal discounting

As has been described, increased rates of TD and related clinical symptoms in obese individuals have been associated with reduced activation in prefrontal areas associated with executive function (Kishinevsky et al., 2012; Stoeckel et al., 2013; Weygandt et al., 2013). This is perhaps unsurprising, given the evidence suggesting that impulse control in relation to food-specific tasks relies, at least in part, on cognitive control via the DLPFC (Hare, Camerer, & Rangel, 2009; Hare, Malmaud, & Rangel, 2011). More generally, the ability to resist immediate temptation and exert self-control has been proposed to rely on activity in the right PFC (Knoch & Fehr, 2007) and increased activation in the left DLPFC has been demonstrated during deliberations over delayed reward (i.e. more controlled) choices (Hare, Hakimi, & Rangel, 2014). However, the localisation of key regions in what is quite a complex behaviour is inherently difficult, suggesting that the neural correlates of intertemporal choice behaviour is probably not isolated to one specific region.

Rather, the connectivity between the DLPFC and VMPFC has been associated with discounting behaviour. Whilst areas of the VMPFC have consistently been associated with the encoding of stimulus value and the magnitude of reward, the DLPFC is typically engaged to modulate value signals from the VMPFC, particularly during decisions regarding delayed rewards (Hare et al., 2009; Hare et al., 2014; Weygandt et al., 2013). Additionally, mesolimbic regions such as the nucleus accumbens and ventral striatum have been implicated in the encoding of both immediate and future reward value, whilst areas such as the posterior parietal cortex have been associated with delayed reward choices (Ballard & Knutson, 2009; Kable & Glimcher, 2010; McClure, Laibson, Loewenstein, & Cohen, 2004). Such findings provide evidence for the sensitivity to the value/magnitude of rewards in limbic, goal-directed brain regions, whilst consideration of temporal foresight relies on cortical, cognitive control mechanisms. Moreover, associations have been found between intelligence levels and the activity of both value-dependent and executive function networks during TD tasks in adolescents (Ripke et al., 2014).

Resting state neural activity of these networks have been both associated with, and shown to predict discounting behaviour (Gianotti, Figner, Ebstein, & Knoch, 2012; Li, Ma, et al., 2013). Using EEG recordings and DNA genotyping Gianotti et al. (2012) aimed to assess the role of both baseline neural activation and dopaminergic systems – via the catechol-*O*-methyltransferase (COMT) Val158Met genotype – known to modulate prefrontal dopamine on discounting behaviours. A higher number of Val alleles indicate greater COMT activity and lower dopamine levels. This study showed that COMT has a significant effect on baseline activity in the left DLPFC; a higher number of Val alleles (and thus reduced dopamine levels) was associated with lower baseline activation. Additionally, the number of Val alleles was positively correlated with TD rates whilst activity in the left DLPFC was inversely correlated with discounting rates. Finally, baseline activity of the left DLPFC mediated the effects of COMT on TD (Gianotti et al., 2012). These findings suggest that reduced activity of dopaminergic systems and prefrontal areas may be a neural signature for impaired cognitive control and choice impulsivity.

A recent study of resting state functional connectivity (rsFC), Li, Ma, et al. (2013) reported correlations between TD processes and the activity of distinct neural networks. Within the ‘money’ network, rsFC of areas involved in the encoding of rewards, such as the striatum, were positively correlated with discounting rates and impulsivity. In contrast, the rsFC of frontoparietal areas implicated in the ‘time’ network, i.e. the DLPFC, were negatively correlated with TD. Whilst these findings echo those mentioned previously (Ballard & Knutson, 2009; Kable & Glimcher, 2010; McClure et al., 2004), the functional connectivity between these two networks was inversely correlated with TD behaviour. This suggests that a reduced exchange of information between the two systems may also contribute to increased TD and choice impulsivity. Interestingly, Li, Ma, et al. (2013) also suggest that increased activity in a ‘choice’ network, including frontoparietal networks and the dorsal anterior cingulate cortex-anterior insular cortex, is associated with TD, suggesting that heightened evaluations of the emotional salience of rewards biases less cognitive demand and thus immediate reward choices.

In summary, distinct neural networks are involved in the evaluation of rewards and subsequent choice deliberations. Baseline activity in such regions, as well as the functional connectivity between relevant neural networks also influences rates of discounting. Taken together, these findings suggest neural network based biomarkers of decision making processes such as intertemporal choice behaviour.

The effects of neuromodulation on temporal discounting

Despite a broad amount of research implicating the role of distinct neural networks in intertemporal choice behaviour, only a limited number of studies have investigated the effects of neuromodulation on TD (see Table 4.2). Alongside neuroimaging approaches, neuromodulation techniques may enable causal relationships to be drawn between brain activity and implicit, decision making processes.

Figner et al. (2010) reported the first data on the effects of neuromodulation on TD. Following LF (inhibitory) rTMS to the left (but not right) DLPFC, an increase in the choice of SS rewards was reported. Also, two studies by the same group have looked at the effects of TBS, a form of TMS that uses bursts of high frequency stimulation (i.e. 50Hz), on TD. Continuous TBS, which is thought to suppress neural activity, to the right DLPFC, reportedly reduces the discounting of future rewards, i.e. increasing the ability to delay gratification (Cho et al., 2010) and is accompanied by reduced rCBF in the ipsilateral PFC (Cho et al., 2012). Given the conflicting evidence so far, the role of hemispheric lateralisation and excitatory/inhibitory neuromodulation protocols on TD behaviour remains unclear.

The evidence regarding the effects of HF rTMS on TD is somewhat more consistent. A recent study investigating TD with regards to smoking demonstrated no differences in discounting behaviours between smokers and non-smokers, however following HF rTMS to the left DLPFC both groups demonstrated reduced TD and an increased preference for delayed rewards, i.e. increased ability to delay gratification (Sheffer et al., 2013). Similarly, HF rTMS to the MPFC increased preference for delayed, monetary rewards, which

subsequent PET imaging indicated was associated with dopamine release in the striatum (Cho et al., 2014). The only study, which was conducted by our group, to investigate the effects of tDCS (anode to the right/cathode left DLPFC) on discounting behaviour reported no changes to TD. However, typical discounting behaviour of participants (who were frequent food cravers) moderated the effects of tDCS on the study's primary outcome; individuals who discounted future rewards less (i.e. displayed less choice impulsivity) were more susceptible to the anti-food craving effects of tDCS (Kekic et al., 2014).

In summary, the effect of neuromodulation on discounting behaviour is somewhat unclear. The importance of stimulation parameters needs to be established, since inhibitory neuromodulatory procedures to the PFC have shown to both increase and decrease discounting behaviour. Similarly, the role of hemispheric lateralisation, optimal stimulation protocols and sites are undefined – inhibitory protocols to both the left and right hemisphere have produced opposite effects on TD, whilst rTMS to both medial and DLPFC targets has reduced rates of discounting.

Table 4.2 Studies investigating the effects of neuromodulation on temporal discounting

	N	Sample	Design	Type	Protocol	Area	Task	Findings
Figner et al (2010)	52	HS	Between subjects	rTMS	LF (1 Hz) rTMS i) left LPFC, ii) right LPFC iii) sham 15 mins	Left or right LPFC	SS/LL task;	LF rTMS to the left (but not right) LPFC led to greater discounting.
Cho et al (2010)	7	HS	Within subjects	TBS	3 pulses at 50Hz i) iTBS (excitatory), ii) cTBS (inhibitory) & iii) sham TBS (coil angle)	Right DLPFC	Monetary TD task; <i>k</i> value	cTBS reduced <i>k</i> value/ impulsivity by 37% compared to sham. iTBS did not alter TD.
Cho et al (2012)	8	HS	Within subjects	TBS	3 pulses at 50Hz i) cTBS (inhibitory) continuous trains 40 secs = 600 pulses & ii) sham TBS (coil at angle) + PET imaging	Right DLPFC	As above	cTBS reduced <i>k</i> value/ impulsivity; participants favour LL rewards. Reduced rCBF in ipsilateral DLPFC regions.
Sheffer et al (2013)	66	Smokers (<i>n</i> =47) & non-smokers (<i>n</i> =19)	Within subjects	rTMS	Three HF rTMS sessions; i) 10 Hz, ii) 20Hz, iii) sham.	Left DLPFC	Monetary & cigarette TD tasks	HF rTMS decreased TD of monetary gains, increased TD of monetary losses in both groups.
Cho et al (2014)	24	HS	Within subject	rTMS	10 Hz rTMS 15 trains = 150 pulses/750 pulses + PET imaging	MPFC/vertex	Monetary TD task; <i>k</i> value	rTMS to MPFC reduced TD; preference for delayed rewards. DA release striatum
Kekic et al (2014)	17	Frequent food cravers	Within subjects	tDCS	Anode right/cathode left 2mA for 20 minutes	DLPFC	Monetary TD task; <i>k</i> value	TD moderated the effect of tDCS on food cravings; reduced TD predicted anti-craving effects of tDCS

k values represent an individual's rate of discounting and $> k$ values indicated greater TD; AUC: area under the curve is a theoretically neutral measure of discounting and $< AUC$ indicates greater TD; DLPFC: dorsolateral prefrontal cortex; MPFC: medial prefrontal cortex.

The effects of repetitive transcranial magnetic stimulation on temporal discounting in anorexia nervosa

The literature discussed above, although sparse, suggests that there are identifiable differences in TD behaviour across the spectrum of disordered eating. Specifically, people with disorders associated with over-eating, such as obesity and BED, display increased discounting of future rewards (see Table 4.1) whilst data from one study suggests that individuals with AN demonstrate a unique ability to delay gratification (Steinglass et al., 2012). Moreover, the neural correlates of TD are somewhat understood, implicating limbic and cognitive neural networks and their functional connectivity (Gianotti et al., 2012; Hare et al., 2014).

As has been discussed previously (see Chapter 1), over-representation of interoceptive signals (Cowdrey et al., 2011; Zhu et al., 2012) in conjunction with heightened prefrontal activity has been reported in AN (Uher et al., 2003). Subsequent neuro-circuit based models implicate alterations in such ‘bottom-up’ and ‘top-down’ processing in AN and this is schematically presented in Figure 4.2 taken from Kaye et al. (2009). Whilst this diagram aims to explain the altered neurocircuitry and resulting conflict between aversive interoceptive drives and heightened cognitive control mechanisms in AN, it is also relevant to the concept of TD. Specifically, in response to such conflict, excessive top down control via areas such as the DLPFC, may encourage the resistance of satisfying immediate short-term homeostatic urges (e.g. hunger) in favour of longer-term goals (e.g. staying thin). Moreover, altered functional connectivity between such networks has been demonstrated in AN and may contribute to the disorder’s aetiopathogenesis (Boehm et al., 2014; Cowdrey et al., 2014).

Since the application of rTMS to the DLPFC has been shown to alter TD behaviours (see Table 4.2), rTMS may provide an opportunity to implicitly alter the hypothesised excessive, top-down control and/or the impaired circuitry in AN that leads to the pursuit of weight loss over more immediate and homeostatic needs. Furthermore, the effects of rTMS on TD may underlie the therapeutic effects of rTMS on AN symptoms that have been reported (Kamolz

et al., 2008; McClelland, Bozhilova, Nestler, et al., 2013; Van den Eynde, Guillaume, et al., 2013).

The aim of the research reported in this chapter was to examine TD in AN and the effects of rTMS on this neurocognitive construct. Specifically, the relationship between TD and ED symptoms was explored and it was hypothesised that the restrictive AN subtype group would display reduced TD compared to individuals with a binge/purge subtype diagnoses. Given the symptom improvements reported previously, it was hypothesised that real (as opposed to sham) HF rTMS to the left DLPFC would temporarily increase TD, i.e. individuals would demonstrate a preference for SS rather than LL rewards. Such findings may indicate that a potential neurocognitive biomarker of the effects of rTMS on AN symptoms is the technique's ability to transiently and implicitly alter intertemporal choice behaviour.

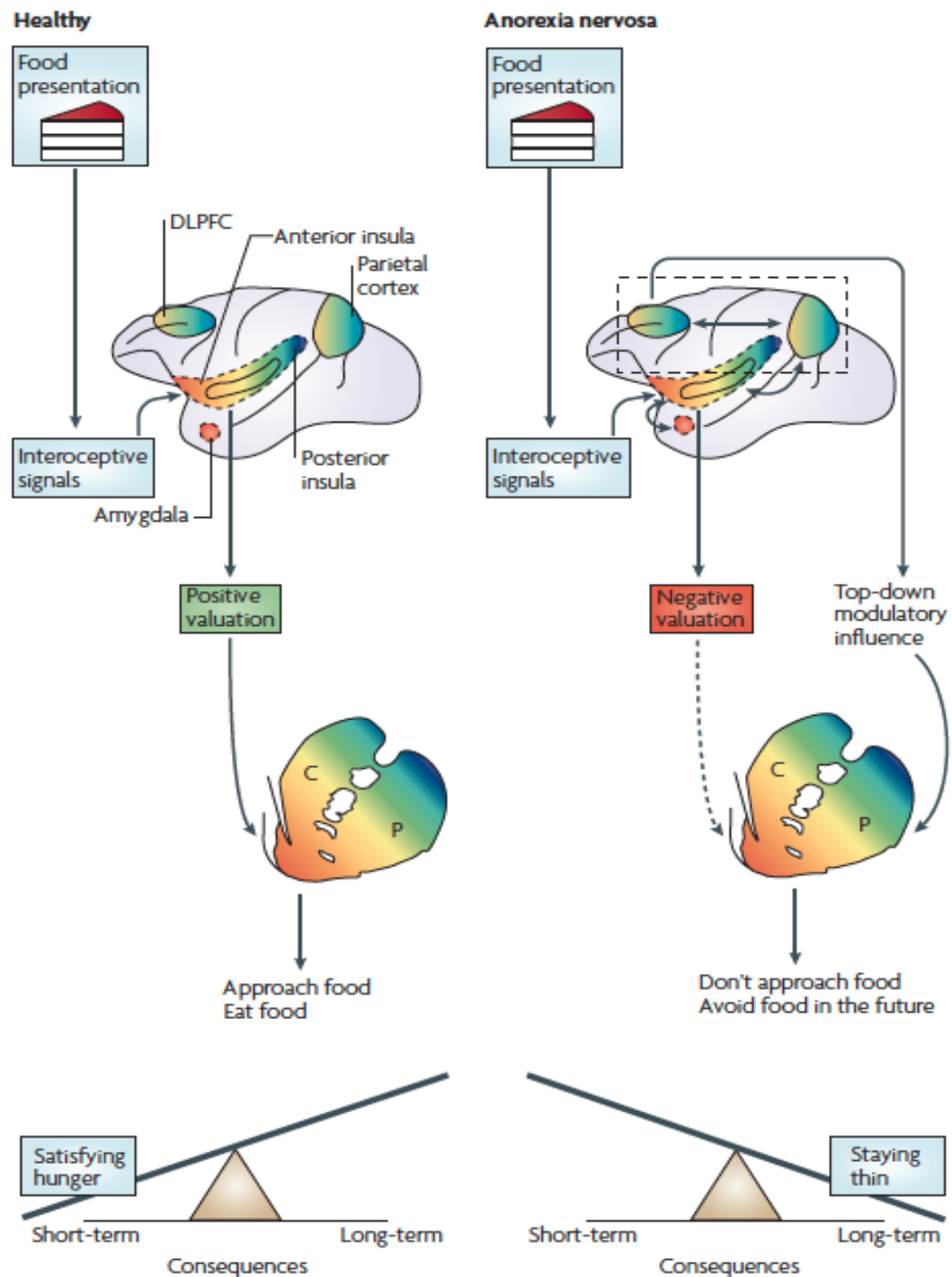


Figure 4.2 Impaired interoceptive and reward processing in AN and the effects on short-term/long-term decision making

This describes the 'top-down' cognitive control exerted in response to aversive interoceptive 'bottom-up' emotive signals in anorexia nervosa (AN). This process is consistent with accounts of reduced TD in AN, in that the short-term homeostatic drives (e.g. satisfying hunger) are forgone in the pursuit of more valued, delayed outcomes (e.g. staying thin). Reprinted as appears in Kaye et al. (2009) with permission from Nature Publishing Group.

Methods

Participants

Recruitment and randomisation procedures have been described in Chapter 3.2.

Procedures

Description of procedures is provided in Chapter 3.2.

Measures

Baseline

Baseline measures have been described in Chapter 3.3.

Outcomes

Temporal discounting

A computerised hypothetical monetary TD task (Rubia, Halari, Christakou, & Taylor, 2009) that measures the degree to which a reward is discounted in relation to its temporal delay was used. Participants choose (by pressing the left or right mouse button) between a smaller amount of money available immediately (between £0 and £100), and a larger amount (always £100) available after 1 week, 1 month, 1 year, or 2 years (25 trials for each delay). Appendix H.2 provides the instructions for the TD task and screen-shot examples of TD choices. The value of the immediate reward is automatically adjusted in an algorithm based on previous choices; this narrows the range of the immediate values offered until an amount is reached that the participant judges as equivalent to the fixed delayed reward (Richards, Zhang, Mitchell, & de Wit, 1999), i.e. the IP/point of subjective equality – when, given the time delay, the SS reward is deemed equal to the LL (£100) reward. An IP is calculated for each of the four delay periods and these are then used to determine a general rate of discounting.

Discounting rates are assessed in two ways, both of which were computed in the current study. Initially, in order to describe the relationship between the

subjective value of a reward as a function of the delay to its presentation, a hyperbolic function was fitted to the indifference points for each delay (Richards et al., 1999). The mathematical expression for this relationship is $V = A/(1+kD)$, where V is the subjective value, A is the reward amount, D is the delay until receipt and k represents the slope of TD, and thus is a constant which characterises an individual's rate of discounting. The value of k can range from 0 to 1 and is often used as the dependent variable of TD tasks. Participants with **larger k values (i.e. steeper slope of discounting) show greater TD** – they tend to choose SS over LL rewards – and are expected to be more impulsive.

The use of such simple hyperbola in describing TD behaviour is associated with interpretative and statistical difficulties. Instead, AUC measurements of discounting provide theoretically neutral accounts of TD and are therefore more appropriate for investigations with quantitative, inferential statistics (Myerson et al., 2001). A general measure of discounting can be produced from calculating the area under the empirical discounting function. Values are standardised via expressing both the subjective value and the time delay as a proportion of the total value and maximum delay respectively. The AUC is then calculated by plotting the standardised subjective value of rewards against the respective time delay and summing the trapezoids (see Figure 4.3).

The equation used to establish the area of each trapezoid is $(x_2 - x_1)*[(y_1 + y_2)/2]$ where x_2 and x_1 are the successive delays and y_1 and y_2 are the subjective values associated with these delays. The delay periods are expressed as the proportion of the maximum delay period (2 years) i.e. 1 week = 1/104, 1 month = 1/24, 1 year = 0.5 and 2 years = 1 and the standardised subjective values were used for each relevant delay period. Therefore, the AUC outcome of TD has a value between 0 and 1 and **smaller AUC values represent greater rates of discounting** and thus more impulsive decision making.

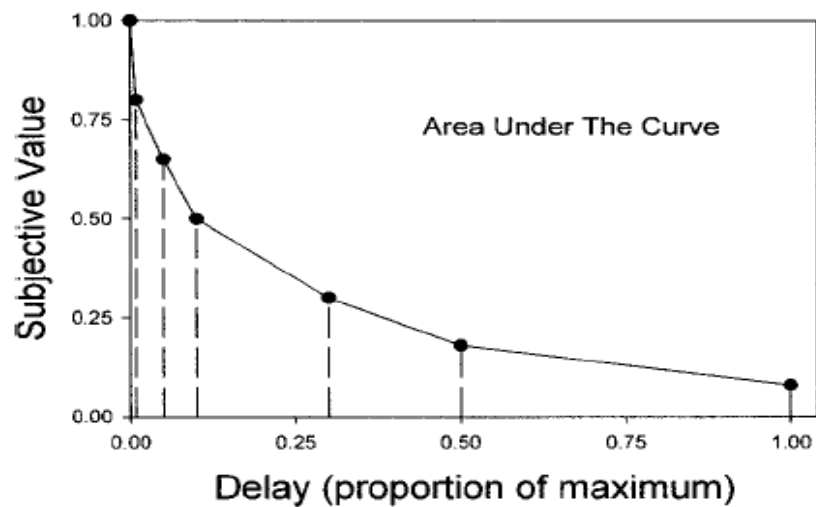


Figure 4.3 Calculation of area under the curve.

The indifference point (IP)/subjective value i.e. when a larger, delayed reward is deemed equal to a smaller, immediately available reward (expressed as a proportion of the maximum reward value available) is plotted against the various time delays (also expressed as a proportion of the maximum delay period). Smaller area under the curve (AUC) indicates greater temporal discounting. Reprinted as appears in Myerson (2001) with permission from John Wiley and Sons.

Statistical analysis

Statistical analyses were performed using IBM® SPSS® software (Version 22). Following consultation with a statistician, when normality or other ANOVA assumptions such as homogeneity of were violated (assessed via Kolmogorov-Smirnov and Levene's statistics respectively) log transformations or other non-parametric alternatives were employed. When Mauchly's test of sphericity was violated, Greenhouse-Geisser corrections are reported. All tests were two-tailed and the level of significance was set at $\alpha = 0.05$.

The k values were non-normally distributed and highly skewed, whilst the AUC data were normally distributed. Therefore, AUC was seen as a preferable alternative for the main analyses (Myerson et al., 2001). However, in order to assess agreement between the two measures of TD – k values and AUC – non-parametric correlational analyses (Spearman's r_s) were conducted.

Pearson's correlations were used to examine associations between AUC/TD and both demographic information and psychopathology (e.g. EDE-Q, DASS-21, VAS). Additionally, independent t-tests were used to compare initial rates of TD (AUC of the TD task pre real/sham rTMS) between education levels (those who had reached primary versus tertiary education levels) and AN subtypes.

The main effect of real versus sham rTMS on rates of TD, as indicated by AUC, was evaluated using a mixed ANOVA (group: real/sham rTMS x time: TDpre, TDpost). Paired-samples t-tests were used to examine the effects of rTMS within each real and sham group separately, and moreover, within the subtypes within each real/sham rTMS groups. Additionally, whether (or not) TD behaviour influences the effects of rTMS on the primary outcome of the RCT, i.e. core AN symptoms (see Chapter 3.3) was also examined: along with symptoms at TP2, the AUC of the first TD task was added as a covariate to the main analysis of rTMS on core AN symptoms, i.e. real/sham rTMS x time (e.g. TP3, TP4, TP5).

Partial eta squared (η^2) and Cohen's d effect sizes are reported for mixed ANOVAs and independent sample t-tests respectively. Partial eta squared (η^2) and Cohen's d effect sizes are reported for mixed ANOVAs and t-tests respectively. Partial eta squared is automatically computed within SPSS by dividing the sums of squares for the effect of interest by the total sums of squares i.e. $\eta^2 = SS_{between}/SS_{total}$ (Levine & Hullett, 2002). Cohen's d was computed by dividing the difference in means by the pooled standard deviation i.e. $d = M_1 - M_2 / \sqrt{(SD_1^2 + SD_2^2) / 2}$. Interpretation of the magnitude of η^2 is 0.01-0.06 = small; 0.06-0.14 = medium and > 0.14; large; and for Cohen's d effect sizes 0.15-0.40 = small; 0.4-0.75 = medium and > 0.75: large (Cohen, 1988).

Results

The same 49 right-handed, female individuals described above (Chapter 3.3), randomised to real ($n = 21$, restrictive-AN = 13, binge/purge-AN = 8) and sham ($n = 28$, restrictive-AN = 15, binge/purge-AN = 13) were included in the subsequent analyses.

Baseline characteristics

Baseline demographic and ED characteristics are described in Chapter 3.3 and reported in Table 3.2.

Outcomes

As expected, Spearman's correlations indicated an inverse relationship between k and AUC values at both time points, pre [$r_s = -0.78, p < 0.001$] and post [$r_s = -0.79, p < 0.001$] real/sham rTMS, confirming their agreement in measuring TD.

Temporal discounting and eating disorder symptomatology/diagnosis

There was a significant inverse correlation between age and AUC [$r = -0.34, p = 0.018$] and whilst BMI at time of assessment was not correlated with AUC, there was a trend for participants' lowest reported BMI to be negatively correlated with AUC [$r = -0.25, p = 0.080$]. Therefore, since smaller AUC represents increased TD, younger age and lower historical BMI were associated with reduced rates of TD, i.e. a tendency to choose LL rewards. There were no significant correlations between AUC and either ED or general psychopathology. Independent sample t-tests indicated no initial difference in AUC between those who reached primary ($n = 27$) or tertiary ($n = 22$) education levels [$t(47) = 0.76, p = 0.448, d = 0.22$], or between the restrictive ($n = 28$) and binge/purge ($n = 21$) AN subtypes [$t(47) = 0.12, p = 0.904, d = 0.03$].

The effect of repetitive transcranial magnetic stimulation on temporal discounting in anorexia nervosa

When comparing the effects of real versus sham rTMS on TD within this AN sample, there was a trend towards a significant interaction effect [$F(1) = 3.71, p = 0.060, \eta^2 = 0.07$] (Figure 4.4). Paired sample t-tests suggest that real rTMS significantly increased AUC/decreased TD [$t(20) = -3.16, p = 0.005, d = 0.54$] (Figure 4.5) whilst sham rTMS had no effect on TD [$t(27) = -0.71, p = 0.485, d = 0.08$] (Figure 4.6). Moreover, paired sample t-tests for each AN subtype within the real rTMS groups indicated that the effect of rTMS was most significant within the restrictive AN subtype [$t(12) = -2.91, p = 0.013, d = 0.54$] but was

non-significant when the effects of real rTMS on the binge/purge AN subtype was considered alone [$t(7) = -1.47, p = 0.185, d = 0.51$] (Figure 4.7). The effects of sham rTMS on TD were non-significant within the restrictive [$t(14) = -0.02, p = 0.986, d = 0.00$] and binge/purge subtypes [$t(12) = -0.88, p = 0.395, d = 0.16$].

When controlling for core AN symptom scores at TP2 and initial AUC (from the preTD task), there were no interaction effects between group (real/sham rTMS) and AN symptoms over time (TP3, TP4, TP5). However, the addition of the preTD AUC score as a covariate accounted for a significant amount of variance in core AN symptoms over time [$F(1.35) = 4.06, p = 0.036, \eta^2 = 0.08$]. Moreover, when controlling for preTD AUC scores, the between group differences (real/sham rTMS) outlined in Chapter 3.3 became significant [$F(1) = 4.29, p = 0.044, \eta^2 = 0.09$]. Given this, a repeated measures ANOVA was conducted separately for each real/sham rTMS group. Controlling for AN symptoms scores at TP2 and AUC scores from the preTD task, there was a significant association between the initial TD covariate and core AN symptoms over time within the real [$F(2) = 3.73, p = 0.034, \eta^2 = 0.17$], but not the sham group [$F(1.20) = 1.49, p = 0.237, \eta^2 = 0.06$].

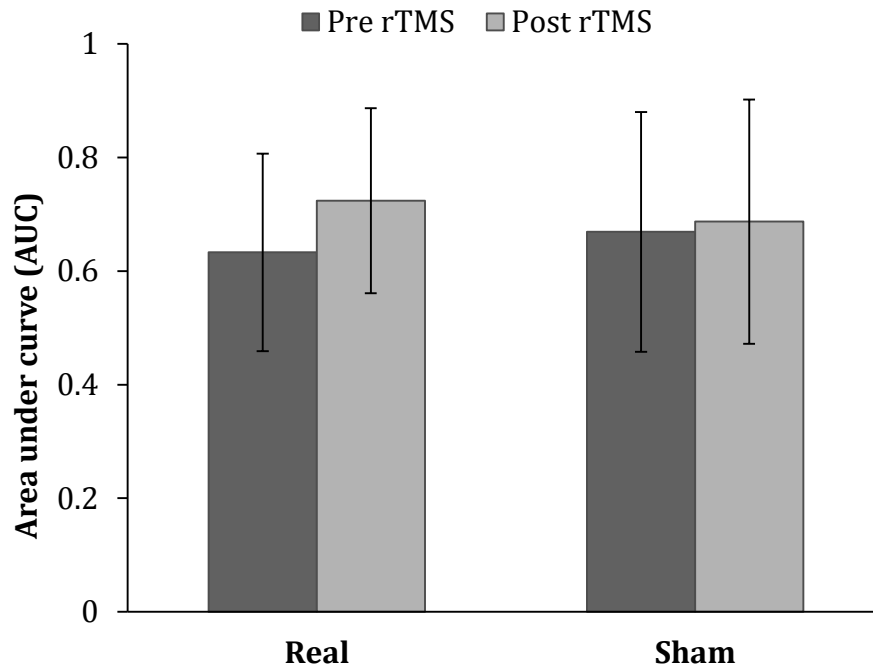


Figure 4.4 Area under the curve pre and post real/sham rTMS. Mean + SD reported.

Real ($n = 21$), sham ($n = 28$).

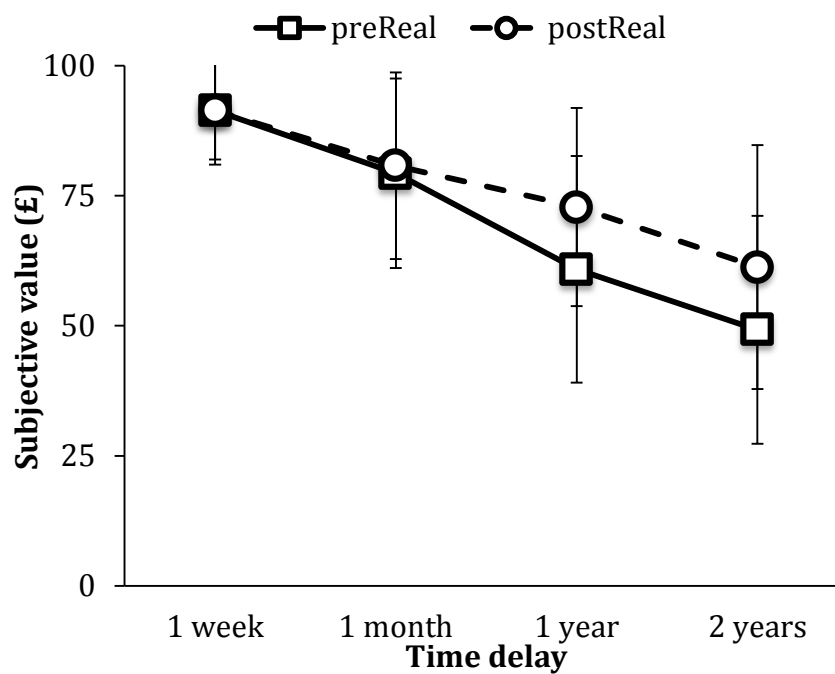


Figure 4.5 Subjective value of reward over time pre and post real rTMS.

($n = 21$)

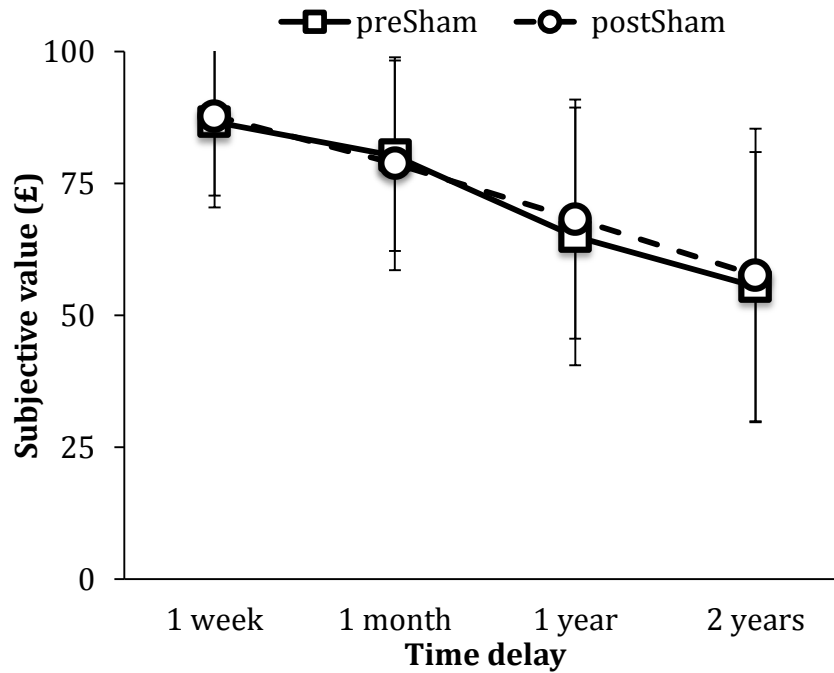


Figure 4.6 Subjective value of reward over time pre and post sham rTMS
($n = 28$)

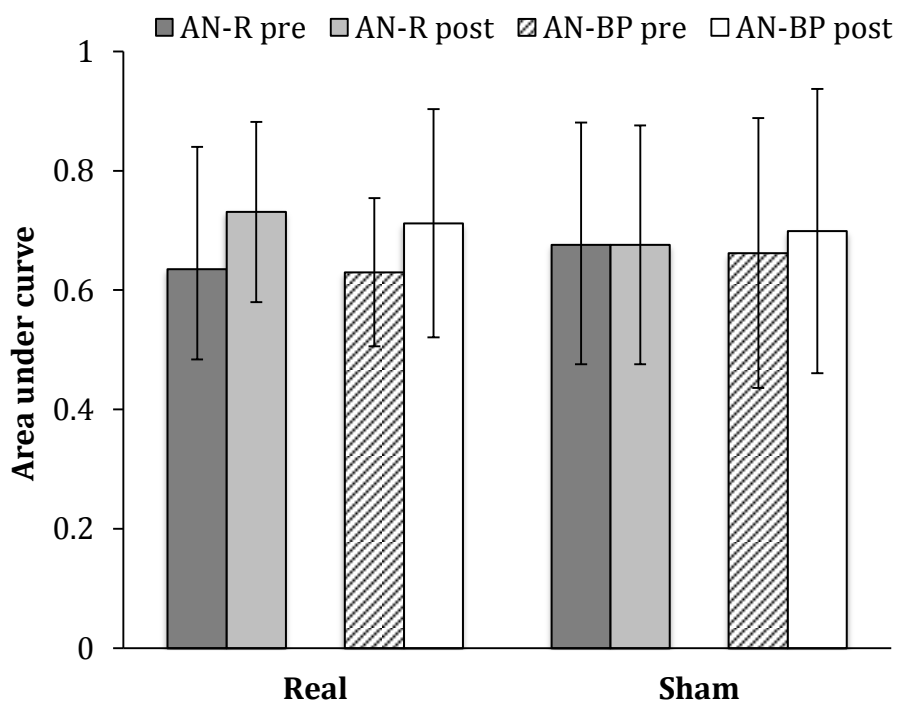


Figure 4.7 Area under the curve for each AN subtype pre and post real/sham rTMS. Mean + SD reported.

R: restrictive, BP: binge/purge. Real ($n = 21$; restrictive = 13, binge/purge = 8), sham ($n = 28$; restrictive = 15, binge/purge = 13).

Discussion

The results of this study, investigating TD in AN and the effects of rTMS on this construct, partially support our initial hypotheses. There was no association between TD and psychopathology; however, lowest BMI since the onset of AN was associated with reduced rates of TD. There were also no differences in TD depending on education history or between restrictive and binge/purge AN subtypes. However, real rTMS altered TD behaviour whilst sham rTMS did not. Yet, the direction of change was the opposite to what was predicted; HF rTMS to the left DLPFC decreased discounting behaviour and thus encouraged delayed gratification in AN. Moreover, this effect was most pronounced in the restrictive AN subtype. Finally, rates of TD prior to rTMS accounted for a significant amount of the variance of the effects of real (but not sham) rTMS on AN symptoms over time.

Our data are somewhat inconsistent with existing literature. In this sample of individuals with AN, we found that age was inversely correlated with AUC, i.e. younger individuals discount future rewards less and therefore displayed less choice impulsivity. In contrast, others report that TD and impulsivity decreases with age related maturation of relevant neural circuitry (Christakou, Brammer, & Rubia, 2011; Steinberg et al., 2009). However, these studies were in younger samples than ours, where impulsivity was highest amongst adolescents. In comparison, all of our participants were adults. Whilst the discrepancies in findings may be due to such differences in the samples studied, they could equally suggest that discounting in AN does not following typical progression with age.

Furthermore, unlike Steinglass et al. (2012), we failed to differentiate TD behaviours between AN subtypes. Additionally, our data suggest that the tendency to choose LL rewards (i.e. increased self-control) is associated with AN individuals' lowest reported BMI, whilst Steinglass et al. (2012) reported that higher BMI was associated with LL reward choice. These differences may be partly due to variation in TD tasks and thus the measurement of TD. The way in which reward choices are framed and how discounting rates are computed

are just two parameters that vary between studies and may therefore explain inconsistencies in findings. Moreover, our participants had particularly enduring forms of AN whilst Steinglass et al. (2012) does not report data regarding illness duration.

In relation to the effects of rTMS on discounting behaviour, our results are consistent with the existing relevant literature. Whilst Figner et al. (2010) increased rates of TD with LF rTMS to the left DLPFC, our findings of reduced TD are in accord with others who applied HF rTMS to PFC regions (Cho et al., 2014; Sheffer et al., 2013). However, the reported decrease in discounting behaviour following inhibitory, cTBS to the right DLPFC is not consistent with the rTMS literature, which is likely to be due to differences between the two neuromodulatory techniques and/or samples studied. Interestingly, we also partially replicated our previous findings in that discounting behaviour explained some of the effects of real (but not sham) non-invasive neuromodulation on ED related symptoms (Kekic et al., 2014). Finally, to our knowledge, this is the first study to report rTMS induced neurocognitive changes within an ED sample.

Mechanistic hypotheses

Given the literature in relation to discounting in AN (Steinglass et al., 2012) and the effects of rTMS on TD (Figner et al., 2010), the hypothesis underpinning this study i.e. that rTMS would reduce exaggerated cognitive control in AN is reasonable. Whilst the findings by Figner et al. (2010) support the notion that LF rTMS applied to the left DLPFC may encourage choice impulsivity in AN, our hypothesis was based on the fact that HF rTMS led to symptom improvements, including reductions in the urge to restrict – which could be argued as symptom exemplifying excessive ‘self-control’ (Kamolz et al., 2008; McClelland, Bozhilova, Nestler, et al., 2013; Van den Eynde, Guillaume, et al., 2013). Moreover, the present study contributes further to this evidence for AN symptom reductions following HF rTMS to the left DLPFC, whilst at the same time demonstrating reductions in discounting behaviour/increases in cognitive control mechanisms (see Chapter 3.3). Therefore, aspects of the neural mechanisms of AN are likely

to be more complex than the proposed over-active prefrontal activity underpinning increased cognitive/self-control hypotheses. Alternatively, rTMS may alter the cortico-striatal circuitry proposed to underlie and thus improve the management of compulsive, habitual behaviours such as food restriction (Godier & Park, 2014; Park et al., 2014).

Alternatively, increased right-sided prefrontal activity has differentiated recovered from currently ill AN individuals and has been associated with good outcomes (Uher et al., 2003). Similarly, increased functional connectivity through reward and prefrontal regions has been associated with better outcomes of rTMS in depression (Downar et al., 2014; Salomons et al., 2014) and increased functional connectivity of relevant value encoding and cognitive appraisal circuitry has been associated with reduced TD (Li, Ma, et al., 2013). Therefore, HF rTMS may facilitate connectivity and the exchange of information between the altered circuitry implicated in AN and may facilitate control over AN related symptoms/compulsive behaviours rather than reduce excessive self-control per se.

Strengths

To date, the effects of rTMS on TD in AN have not been reported. As stated, this RCT was conducted according to strict and robust eligibility and randomisation procedures, and employed state-of-the-art methodologies. This is important to identify potential biomarkers and underlying mechanisms of therapeutic response to rTMS. Given the findings, this study helps to further the debate on the neural mechanisms of AN and the utility of brain directed treatments such as rTMS in this treatment resistant patient population.

Limitations

We could not account for differences in income on TD within this sample. Given the monetary nature of the TD task employed, this may have compromised our findings. In terms of the TD task itself, the way in which choices are framed (accelerate/delay, gains/losses) is suggested to affect rates of discounting, and may account for differences between studies (Steinglass et al., 2012). Our TD

task was previously used to measure impulsive behaviours/conditions (Richards et al., 1999; Rubia et al., 2009) and choices are only framed in one way. This may reduce its ability to capture TD characteristics and the effects of rTMS on these within individuals/conditions that display the opposite, i.e. increased ability to delay gratification, such as AN.

Future directions

Future studies that assess TD across the spectrum of ED are needed in order to ascertain variability in the construct across and within diagnoses. Similarly, studies that compare neuromodulation protocol parameters are required in order to more fully understand the neural correlates of discounting behaviour and develop tailored neuromodulation protocols. Studies comparing different rTMS protocols, i.e. HF versus LF, right versus left DLPFC, may shed light on issues that require further clarification such as neuromodulation mechanisms and the role of hemispheric lateralisation. Specifically, whether or not LF rTMS to the DLPFC alters both TD and AN symptoms in the same way to those reported here is worth investigating.

Summary

These findings suggest that in individuals with AN, real rTMS reduces the discounting of future rewards (i.e. reduces choice impulsivity). Therefore, the effects of rTMS on the neural correlates of self-control in AN may underlie associated improvements in symptoms.

**Chapter 5. A therapeutic case series of repetitive transcranial
magnetic stimulation in five cases of enduring anorexia
nervosa**

Introduction

Anorexia Nervosa (AN) is a life-threatening mental illness. It is characterised by an intense fear of food, eating and gaining weight resulting in severe food restriction and extremely low body weight. Consequently, AN is associated with a myriad of physical and psychological co-morbidities and severely impaired quality of life. Mortality and disability rates are high (Arcelus et al., 2011). The median duration of AN is five to seven years (Zipfel et al., 2000) and given the typically adolescent onset, the illness blights a key developmental period. A quarter of sufferers have a particularly severe and enduring form of the illness that last longer than 10-15 years (Steinhausen, 2002). There is uncertainty about the management of adult patients with AN per se (Schmidt et al., 2012; Watson & Bulik, 2012), especially in those with a severe and enduring form of the illness who have typically undergone multiple psychological and pharmacological treatments and unsuccessful attempts to restore a healthy weight in in-patient treatment (Hay et al., 2012). This situation underscores the need to develop new treatments.

The neurocircuitry of anorexia nervosa

Significant advances have been made over the last decade in our understanding of the neural correlates of AN, with research highlighting both structural (Frank, Shott, Hagman, & Mittal, 2013; Mainz et al., 2012; Van den Eynde, Suda, et al., 2012) and functional (Brooks et al., 2011; Frank & Kaye, 2012; Kim et al., 2012; Pietrini et al., 2011; Uher et al., 2004; Zhu et al., 2012) differences in the brains of AN sufferers compared to controls. Generally speaking, such neuroimaging studies demonstrate grey and white matter alterations, disturbances in limbic, frontal and parietal areas, in addition to alterations in the functioning of neurotransmitters including serotonin and dopamine at different stages of AN.

Drawing from such findings, AN has been proposed in Chapter 1 and by many others as a neuro-circuit based disorder (Kaye et al., 2009; Kaye et al., 2011; Marsh, Maia, et al., 2009; van Kuyck et al., 2009). These neural models propose that the self-regulation difficulties of AN, in particular disturbances in emotion regulation, appetite and self-control, arise from alterations in the activity of

ventral, mesolimbic areas and dorsal, cognitive control circuitry. For example, alterations in reward processing and fear responses have been found in AN (Cowdrey et al., 2011; Holsen et al., 2012; Titova et al., 2013). These 'bottom-up' processing abnormalities may contribute to the heightened emotionality surrounding food, body image and other pertinent cues. In response, altered 'top-down' activations from areas such as the DLPFC (Brooks et al., 2011; Uher et al., 2003; Uher et al., 2004) may be an attempt to modulate dysphoric mood and underlie the characteristic rigidity and extreme self-control of AN.

Repetitive transcranial magnetic stimulation in psychiatry

The DLPFC plays an important role in executive function and cognitive control mechanisms, such as decision making (Plassmann, O'Doherty, & Rangel, 2007) and emotion regulation (Ochsner & Gross, 2007). Given this, the DLPFC is a common target for neuromodulation interventions in other neuro-circuit based, psychiatric disorders. Most notably, rTMS to the left DLPFC has demonstrated clinical efficacy and is approved by the FDA as a second-line treatment for depression (Gaynes et al., 2014; O'Reardon et al., 2007). Evidence suggests that rTMS for depression is most effective as a monotherapy and for treatment-resistant cases. In terms of efficacy, rTMS remains inferior to ECT, although rTMS is associated with far fewer side effects (Slotema et al., 2010). Preliminary evidence exists for the efficacy of rTMS in other neuro-circuit based disorders such as schizophrenia, autism, epilepsy, Parkinson's disease and addictive disorders (Jansen et al., 2013; Slotema et al., 2010; Wassermann & Lisanby, 2001).

Repetitive transcranial magnetic stimulation in eating disorders

Research involving rTMS in ED is in its infancy. However, existing evidence from animal models, human samples and a small number of studies in ED suggests potential for altering ED psychopathology and body weight (see Chapter 2 or McClelland, Bozhilova, Campbell, et al., 2013). To date, two studies investigating the effects of rTMS on ED related symptoms in healthy participants (e.g. food cravings) and five studies in BN exist. Reductions in food cravings following real rTMS have been demonstrated (Uher, Yoganathan, et al., 2005), whilst using an

improved sham method Barth et al. (2011) suggested no effects of rTMS on food cravings. In clinical samples, individual case reports support the therapeutic efficacy of rTMS in BN (Downar et al., 2012; Hausmann et al., 2004). However the only repeated session (15 sessions) RCT of real/sham rTMS within an ED sample suggests no difference between real/sham groups in improving symptoms of BN – both real/sham groups demonstrated equal improvements (Walpoth et al., 2008). Although, this study may have been underpowered (given its small sample size of $n=14$) or may not have delivered enough sessions (given that 20 sessions are typically in protocols for depression). Since then, our group demonstrated that a single session of real, as opposed to sham, rTMS reduced the urge to eat and subsequent binge-eating episodes in patients with BN (Van den Eynde et al., 2010). Therefore, data regarding the therapeutic efficacy for rTMS in BN is mixed but nevertheless promising.

Support for the use of rTMS in AN comes from a successful case report where 20 sessions of rTMS to the left DLPFC treated depression and improved co-morbid ED symptoms (Kamolz et al., 2008). Since then, our group has conducted a non-controlled pilot study of a single session of real rTMS to the left DLPFC in ten AN individuals and demonstrated reductions in levels of anxiety, feeling full and feeling fat – some of the core characteristics of the illness (Van den Eynde, Guillaume, et al., 2013). To our knowledge Chapter 3 of this thesis is the only RCT of rTMS in a moderate sized sample of individuals with AN, and findings suggest that following real (as opposed to sham) rTMS, core symptoms of AN are reduced. However, extrapolating these findings into any long-term therapeutic benefit requires repeated session protocols and longer follow-ups.

Moreover, there is a need to identify biomarkers of response to rTMS (Fidalgo et al., 2014). As is discussed in the previous chapter, individuals with AN have demonstrated reduced TD, specifically the ability to delay gratification, and this has been argued to contribute to their extreme control over food/eating (Steinglass et al., 2012). Following LF rTMS to the left DLPFC, Figner et al. (2010) reported increases in choice impulsivity (i.e. choosing smaller, immediately available awards). Therefore, rTMS may alter intertemporal choice behaviour which may contribute to symptom improvements in AN.

Based on the neuroscience data summarised in Chapter 1 and the ability of rTMS to improve ED related symptoms including preliminary evidence in AN (Kamolz et al., 2008; Van den Eynde, Guillaume, et al., 2013) we aimed to explore the therapeutic utility, i.e. the long-term benefits of repeated sessions of rTMS in AN. Moreover, we utilised improved investigatory techniques than used previously, i.e. neuronavigation (MRI-guided rTMS) and also examined associated changes to TD behaviour. Our primary hypotheses were that 20 session of rTMS would i) improve ED psychopathology and mood, ii) lessen exaggerated cognitive-control (i.e. increase TD) and iii) encourage weight gain.

Methods

Participants

Five participants with a DSM-5 (A.P.A., 2013) diagnosis of AN volunteered to take part in the study. Participant 1 and Participant 5 suffered from restrictive AN with purging (vomiting) behaviours, Participant 2 and Participant 3 met binge/purge AN criteria and Participant 4 had AN-restrictive type. Participants were recruited following their participation in the previous, single session RCT (Chapter 3). Contraindications to rTMS were checked with the TMS Adult Safety Screening Questionnaire (see Appendix E.5 or Keel et al., 2001). Upon taking part in the RCT, participants met the principal eligibility criterion required of a BMI between 14-18.5 kg/m² (one participants BMI rose to above 18.5 between taking part in the RCT and starting this therapeutic trial). Exclusion criteria were being on a dose of psychotropic medication that had not been stable for at least 14 days prior to enrolment, pregnancy, and excessive nicotine use or substance dependence. Local ethical committee approval was obtained (REC ref: 12/LO/1525) and written informed consent was obtained from all participants. The participant information sheet and consent form for this trial are included in Appendices C.2 and D.2 respectively.

Study protocol

Initially, three sessions per week were administered (Monday, Wednesday, Friday) and Participants 1 and 2 attended three rTMS sessions per week for the

first two weeks/six sessions. However, following participants request and in order to adhere more closely to the therapeutic use of rTMS in other disorders (e.g. depression), session frequency was increased to five sessions per week (Monday – Friday) for all participants. Participants 3 – 5 attended five sessions per week throughout. The study protocol is detailed in Table 5.1 and Table 5.2.

Procedures

All five participants had previously undergone a structural magnetic resonance imaging (MRI) scan as part of their participation in the single session RCT and the full details of this procedure are provided in Chapter 3.2. Likewise, the MRI was used with Brainsight® to neuronavigate the TMS coil to the left DLPFC using the Talaraich co-ordinates $x = -45$, $y = 45$, $z = 35$, reported by Fitzgerald et al. (2009) to enhance response to rTMS treatment in depression.

A Magstim Rapid device (Magstim, Whitland, Wales, United Kingdom) using a real TMS figure of eight coil was used to establish participants' MT through peripheral EMG. The motor cortex was identified via the brain scan on the Brainsight software and upon mapping the M1 'hot-spot', MT was defined as the minimum stimulus required to evoke 5 out of 10 MEP greater than 50 μ V. This procedure was repeated every Monday to ensure rTMS was delivered accurately. To administer the rTMS, a Magstim Rapid device and figure-eight coil (Magstim, UK) was also used as described previously (see Chapter 3) in **20 x 5 second trains and 55 second intervals at a frequency of 10Hz, intensity of 110% MT delivering 1000 pulses over 20 minutes each session.** Therefore, during 20 sessions of rTMS a total of 20,000 pulses were administered.

Table 5.1 Protocol for the 20 rTMS sessions and follow-ups

			Weekly	Each session
Week 1	1	M	Height, weight, MT, DASS-21, EDE-Q, TD task	Cue video Pre VAS rTMS Cue video Post VAS
	2	T		
	3	W		
	4	T		
	5	F		
Week 2	6	M	Weight, MT, DASS-21	
	7	T		
	8	W		
	9	T		
	10	F		
Week 3	11	M	Weight, MT, DASS-21	
	12	T		
	13	W		
	14	T		
	15	F		
Week 4	16	M	Weight, MT, DASS-21	
	17	T		
	18	W		
	19	T		
	20	F	Weight, EDE-Q, DASS-21, TD task	
1 month FU			EDE-Q, DASS-21	
6 month FU			EDE-Q, DASS-21	

MT: motor threshold; DASS-21: 21 item depression, anxiety and stress scale; EDE-Q: eating disorder examination questionnaire; TD: temporal discounting; VAS: visual analogue scale; FU: follow-up.

Quantitative measures

Within session measures

Subjective eating disorder experiences

VAS were completed following cue exposure (i.e. a short film clip of people eating highly palatable foods), both immediately before and after each rTMS session (see Table 5.1). These six 10cm VAS assessed 'levels of stress', 'urge to restrict', 'levels of anxiety', 'urge to exercise', 'levels of feeling full' and 'levels of feeling fat' (see Appendix G.1).

Between session measures

Body mass index

Weight was measured and body mass index (BMI) was calculated before and after the 20 rTMS sessions by dividing participants' weight (kg) by the square root of their height (m²). Whilst BMI is reported at 1 and 6 month follow-up, this was typically calculated using self-reported weight.

Eating disorder symptomatology

The Eating Disorder Examination Questionnaire (EDE-Q, version 6) is described in Chapter 3.3 and included in Appendix F.1.

General psychopathology

The 21 item Depression, Anxiety & Stress Scale (DASS-21) is described in Chapter 3.3 and included in Appendix F.2.

Temporal discounting

The TD task is described in Chapter 4 and included in Appendix H.2.

Qualitative information

Feedback from patients

Qualitative, non-structured and non-specific feedback from patients was recorded in an informal manner throughout and following the 20 rTMS sessions.

Feedback from carers, partners, parents or friends

In order to gain objective insight and feedback, towards the end of the 20 sessions participants asked someone close to them to complete a form with questions regarding any noticeable changes in the participant. A significant other including a carer, partner, parent and friend commented on each participant's typical ED symptoms, mood and any other relevant information before, during and after the rTMS intervention.

Analyses

As this is a small series of five cases, analyses is limited to descriptive information regarding changes in BMI, EDE-Q and DASS-21 scores and the TD area under the curve outcome (AUC; see Chapter 4). With the exception of the TD task, which was only collected pre- and post-intervention, the other outcomes (BMI, EDE-Q and DASS-21) were recorded at pre-, post-intervention, 1 and 6 month follow-up. Within session VAS assessments are graphically presented in order to examine any patterns/trends within, and across the course of the 20 sessions.

Results

Participants

Demographic and clinical information for participants can be found in Table 5.3. All participants had particularly severe and enduring forms of the illness, with illness duration ranging from 5 – 35 years, multiple failed attempts at other forms of psychological and/or pharmacological treatments and of note, one patient had also tried ECT to treat her AN.

Adverse events

All five participants were due to attend twenty sessions; Participant A, C and D completed all sessions. Participant B missed one of her sessions at the mid-way point due to her reporting a single episode of being dizzy/dazed following a session. Sessions were resumed once vital signs and bloods had been checked and returned as normal. As a result, Patient B only completed 19 sessions of the intended 20. Similarly, Patient E missed her final, twentieth session as a result of being unwell. This was primarily due to dental problems that were unrelated to the rTMS. Patient E also only completed 19 of the 20 intended sessions. To our knowledge, along with the occasional, mild headache/discomfort of rTMS, these were the only adverse events experienced.

Quantitative results

Within session measures

Subjective eating disorder experiences

Where there were missing data (e.g. incomplete answers or missed sessions) the average of the previous and next VAS scores was substituted, or in the case of missing scores on the twentieth session, the previous score was used. Generally speaking, scores across all six VAS measures pre-rTMS were slightly higher than post-rTMS within each session. This relationship is demonstrated in Figure 5.1 - Figure 5.6. Additionally, there was a general decrease in scores across the course of the 20 sessions for all VAS measures.

Table 5.2 Timeline for the 20 rTMS sessions and follow-ups.

2013							2014						
	July	Aug	Sept	Oct	Nov	Dec	Jan	Feb	March	April	May	June	July
A	20 rTMS		1 FU					6 FU		10 top-up rTMS (1 x weekly) 5 top up rTMS (1 x fortnightly)			
B	19 rTMS		1 FU 12 top-up rTMS (each weekday)					6 FU*					
C	20 rTMS				1 FU		6 FU						
D	20 rTMS				1 FU		6 FU						
E	19 rTMS							1 FU		6 FU			

*1 and 6 FU: 1 and 6 month follow-up; *at her request this patient had 12 top-up rTMS sessions between 1 and 6 month follow-ups.*

Table 5.3 Demographic and clinical information for each participant prior to 20 rTMS sessions.

	Age	Lowest BMI	BMI	Age of onset	Illness duration	Anorexia subtype	Diagnosed comorbidities	Current medications	Concurrent treatment	Previous treatment history
A	23	13.5	14.78	12	12 years	R (purging)	Depression	Olanzapine, Diazepam, Fluoxetine	Inpatient	12 years inpatient & ECT
B	52	16.2	16.40	17	35 years	B/P	-	Fluoxetine	-	6 months day care, 3 years outpatient
C	32	15.0	19.24	26	5 years	B/P	Depression	-	-	Outpatient
D	41	13.6	15.35	10	31 years	R	-	-	-	Inpatient & outpatient
E	30	9.8	14.54	12	19 years	R (purging)	-	Fluoxetine	-	6 years inpatient

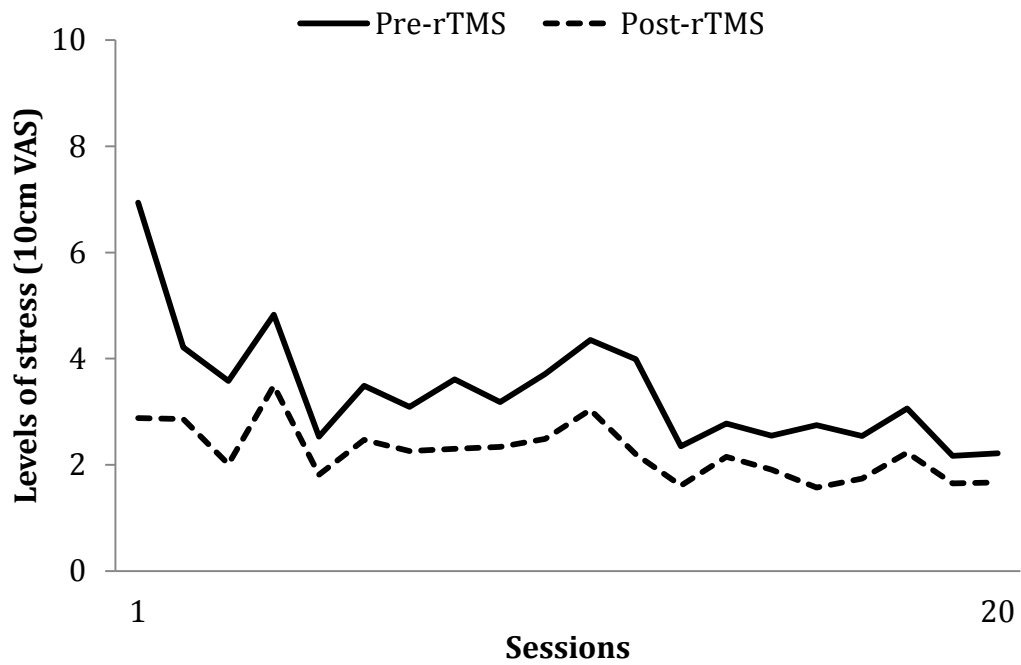


Figure 5.1 Levels of stress; mean VAS scores pre and post each rTMS session.

Visual analogue scale (VAS) scores range from 0 (not stressed at all) to 10 (extremely stressed).

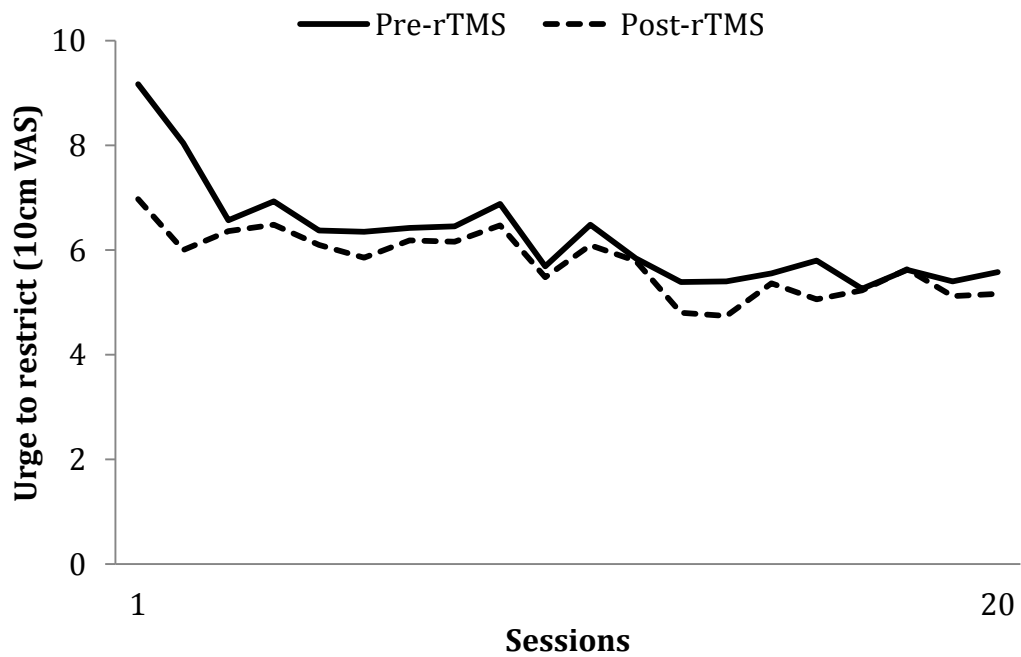


Figure 5.2 Urge to restrict; mean VAS scores pre and post each rTMS session.

Visual analogue scale (VAS) scores range from 0 (no urge to restrict) to 10 (extremely strong urge to restrict).

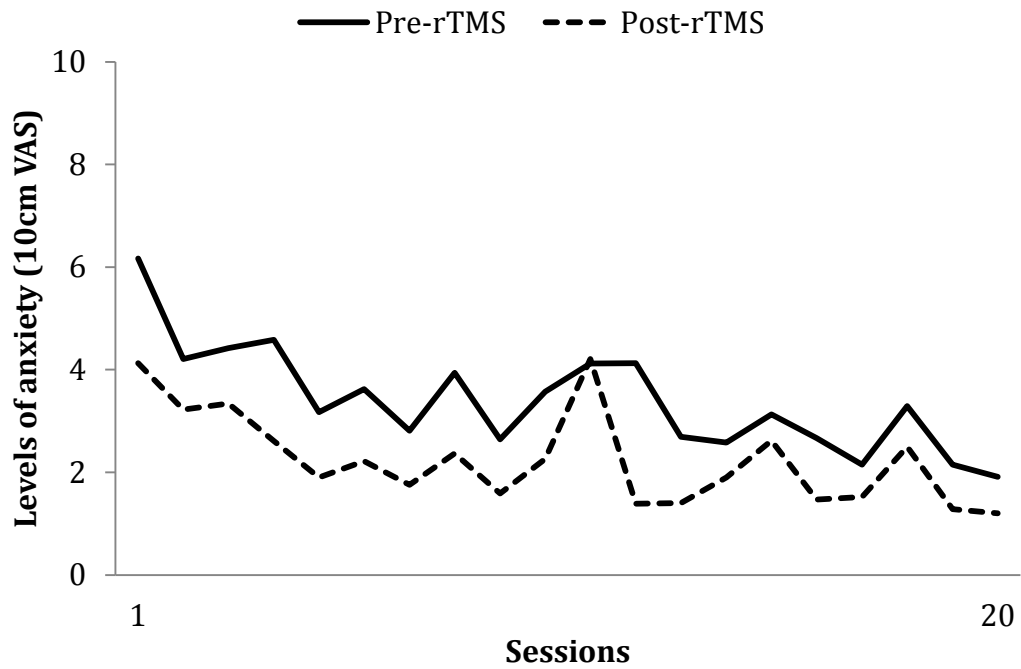


Figure 5.3 Levels of anxiety; mean VAS scores pre and post each rTMS session.

Visual analogue scale (VAS) scores range from 0 (not anxious at all) to 10 (extremely anxious).

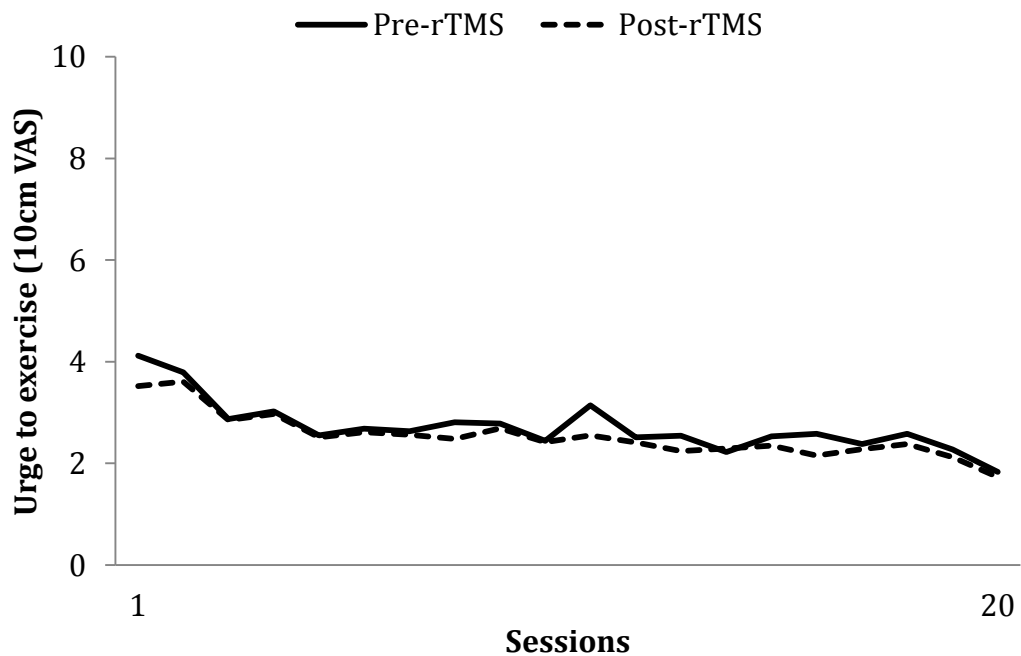


Figure 5.4 Urge to exercise; mean VAS scores pre and post each rTMS session.

Visual analogue scale (VAS) scores range from 0 (no urge to exercise at all) to 10 (extremely strong urge to exercise).

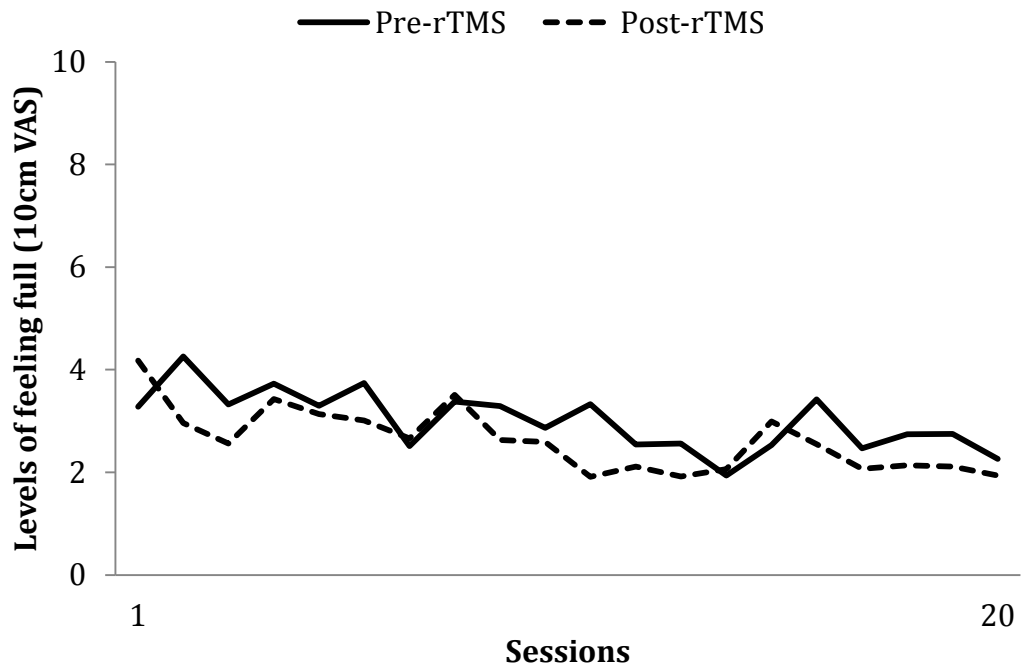


Figure 5.5 Levels of feeling full; mean VAS scores pre and post each rTMS session.

Visual analogue scale (VAS) scores range from 0 (not feeling full at all) to 10 (feeling extremely full).

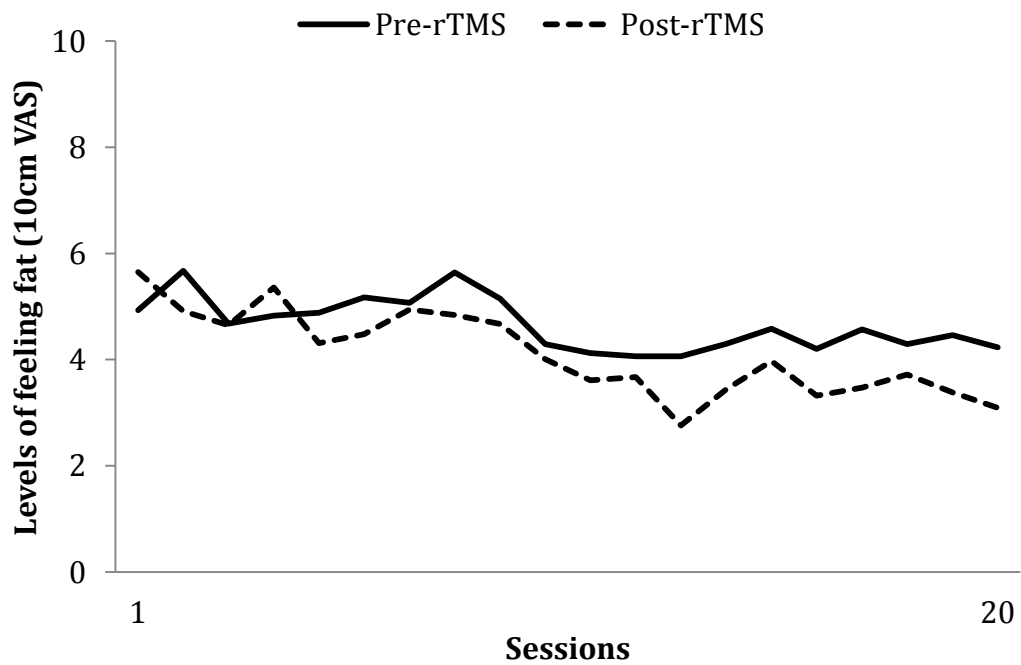


Figure 5.6 Levels of feeling fat; mean VAS scores pre and post each rTMS session.

Visual analogue scale (VAS) scores range from 0 (not feeling fat at all) to 10 (feeling extremely fat).

Between session measures

Body Mass Index

As Table 5.4 suggests, there were no substantial increases in weight and BMI in any of the participants following the rTMS sessions. There was, however, a loss of approximately 2kg in most participants by six-month follow-up.

Eating disorder symptomatology

Individual global and subscale EDE-Q scores are reported in Table 5.4 and Table 5.6 respectively. A sustained improvement in ED psychopathology is demonstrated in most individuals. Average EDE-Q subscale scores across the five participants are presented in Figure 5.7. Mean scores across all subscales decreased following 20 sessions of rTMS and continued to do so at 1 and 6 month follow-up – with the exception of the eating concern subscale which increased at 6 month follow-up, however still remained below baseline. Furthermore, by the end of the 20 rTMS sessions many individual and most average subscale scores fell below 4, therefore no longer meeting levels of clinical significance (Carter et al., 2001; Luce et al., 2008; Mond et al., 2004). Many remained below this at six months following the rTMS intervention. Despite showing a steady decline, average scores for the restraint subscale only fell below 4 at 6 month follow-up. Additionally, by 6 month follow-up, three participants' global EDE-Q scores fell below 2.80, a more stringent and sensitive criteria for clinical significance proposed by Mond et al. (2008).

Table 5.5 reports the frequency of ED behaviours, such as bingeing, vomiting and laxative use reported by participants (via the EDE-Q) across the course of the intervention and at follow-ups. Participant D, AN restrictive subtype, was the only individual without either bingeing or purging behaviours. Whilst Participant A failed to report/quantify the frequency of her vomiting behaviours on the EDE-Q up until her 6 month follow-up, she revealed to researchers that these behaviours had significantly reduced following the rTMS intervention. Patient B reported that the frequency of both her bingeing and vomiting reduced following the intervention along with her misuse of laxatives. Patient C reported extremely high rates of bingeing/purging with little to no changes, or

even increases in vomiting demonstrated. Patient E was AN-restrictive with purging (vomiting) and reported a steady decrease in the frequency of these behaviours over the course of the study.

General psychopathology

Total and subscale DASS-21 scores for each individual are presented in Table 5.4 and Table 5.7 respectively. Average scores across the DASS-21 subscales are presented in Figure 5.8. Scores on the depression and anxiety subscales decreased over time, with a slight increase between 1 and 6 month follow-up, but still remaining below baseline. Mean scores on the stress subscale substantially decreased following the 20 rTMS sessions, with moderate increases at each follow-up, however still remaining much below baseline.

Temporal discounting

Pre and post the 20 sessions of rTMS, the AUC of the TD function remained relatively unchanged in most participants (Figure 5.9). The most substantial change in AUC was demonstrated in Participant C; AUC was much higher following the 20 sessions of rTMS. This indicated that, following the intervention, Participant C was more inclined to wait for larger, delayed rewards. A similar pattern was seen in Participant E, however the difference was not of the same magnitude.

Table 5.4 Individual weight, BMI, EDE-Q global and DASS-21 total scores.

Participant	Weight				BMI				EDE-Q Global				DASS-21 Total			
	Pre	Post	1 FU	6 FU	Pre	Post	1 FU	6 FU	Pre	Post	1 FU	6 FU	Pre	Post	1 FU	6 FU
A	36.90	36.20	34.50	34.50	14.78	14.50	13.82	13.82	4.29	3.01	2.67	2.46	23	11	18	9
B	47.40	47.50	46.20	45.60*	16.40	16.45	15.99	15.78*	4.12	3.46	3.36	2.75*	40	23	21	35*
C	57.60	57.90	57.80	53.52	19.24	19.35	19.31	17.88	3.87	2.35	1.06	2.71	26	6	16	19
D	41.80	41.80	-	38.00	15.35	15.35	-	13.96	5.55	5.55	5.50	4.88	41	14	21	19
E	37.70	-	35.50	36.00	14.54	-	13.69	13.89	5.20	4.57	4.14	3.67	52	35	18	24

*BMI: body mass index; EDE-Q: eating disorder examination questionnaire; DASS-21: 21 item depression anxiety and stress scale; 1 and 6 FU: 1 and 6 month follow-up; *individual had 12 top-up rTMS sessions between 1 and 6 month follow-ups*

Table 5.5 Individual frequencies of eating disorder behaviours.

Participant	Bingeing				Vomiting				Laxative Use			
	Pre	Post	1 FU	6 FU	Pre	Post	1 FU	6 FU	Pre	Post	1 FU	6 FU
A	NA	NA	NA	NA	-	-	-	5	NA	NA	NA	NA
B	10	8	5	8*	10	8	7	8*	15	10	9	12*
C	20	25	20	15	40	50	50	70	NA	NA	NA	NA
D	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
E	NA	NA	NA	NA	28	22	27	10	NA	NA	NA	NA

*1 and 6 FU: 1 and 6 month follow-up; *individual had 12 top-up rTMS sessions between 1 and 6 month follow-ups; NA: not applicable*

Table 5.6 Individual EDE-Q subscale scores.

Participant	Restraint				Eating				Weight				Shape			
	Pre	Post	1 FU	6 FU	Pre	Post	1 FU	6 FU	Pre	Post	1 FU	6 FU	Pre	Post	1 FU	6 FU
A	4.80	4.20	4.20	2.60	2.60	2.60	2.00	2.20	4.40	2.00	1.60	1.80	5.34	3.25	2.87	3.25
B	5.40	6.00	6.00	3.00*	3.80	1.40	1.00	4.20*	3.40	3.80	4.20	1.80*	3.87	2.62	2.25	2.00*
C	4.80	3.20	1.60	4.20	3.80	1.80	1.40	2.80	3.40	2.40	0.00	2.00	3.50	2.00	1.25	1.87
D	6.00	5.40	5.60	5.40	4.40	4.80	4.60	4.60	5.80	6.00	5.80	4.40	6.00	6.00	6.00	5.13
E	5.00	4.60	4.60	3.40	6.00	4.60	3.60	2.80	3.80	3.60	2.60	3.00	6.00	5.50	5.75	5.50

*1 and 6 FU: 1 and 6 month follow-up, * individual had 12 top-up rTMS sessions between 1 and 6 month follow-ups*

Table 5.7 Individual DASS-21 subscale scores.

Participant	Depression				Anxiety				Stress			
	Pre	Post	1 FU	6 FU	Pre	Post	1 FU	6 FU	Pre	Post	1 FU	6 FU
A	4	2	6	0	9	3	5	2	10	6	7	7
B	10	11	7	13*	11	5	5	5*	19	7	9	17*
C	6	0	6	7	6	2	2	6	14	4	8	6
D	9	4	4	2	13	4	3	7	19	6	14	10
E	14	13	7	7	17	11	4	6	21	11	7	11

*EDE-Q: eating disorder examination questionnaire; DASS-21: 21 item depression, anxiety and stress scale; 1and 6 FU: 1 and 6 month follow-up; *individual had 12 top-up rTMS sessions between 1 and 6 month follow-ups.*

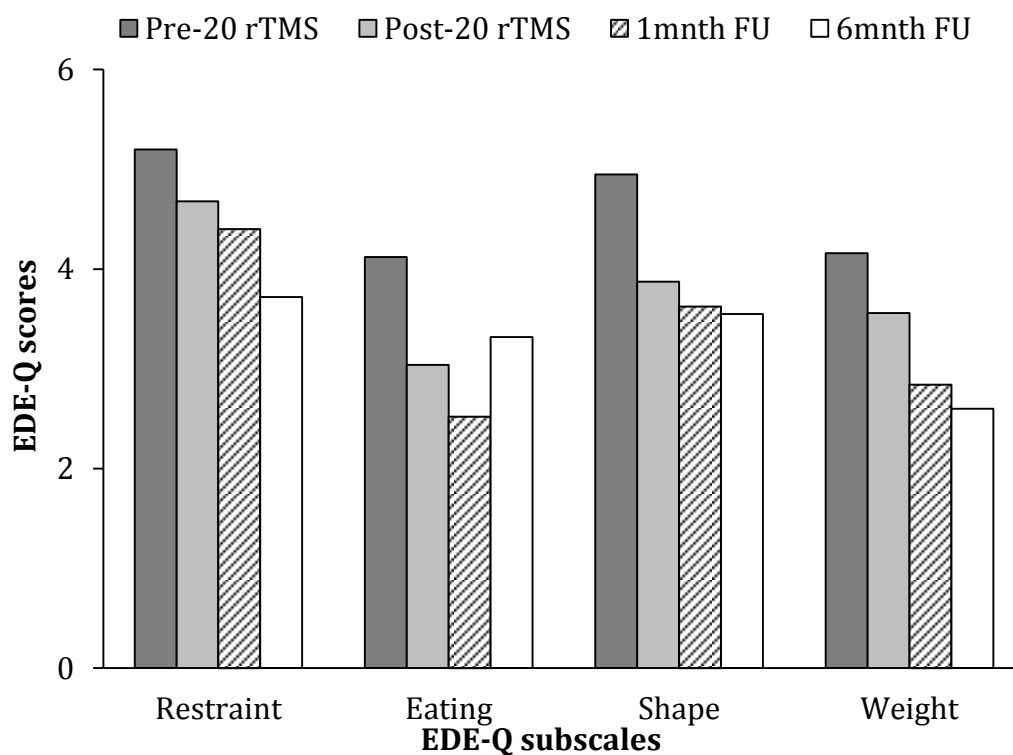


Figure 5.7 Mean EDE-Q subscale scores pre and post the 20 rTMS sessions and at 1 and 6 month follow-up.

EDE-Q: eating disorder examination questionnaire; mnth: month; FU: follow-up

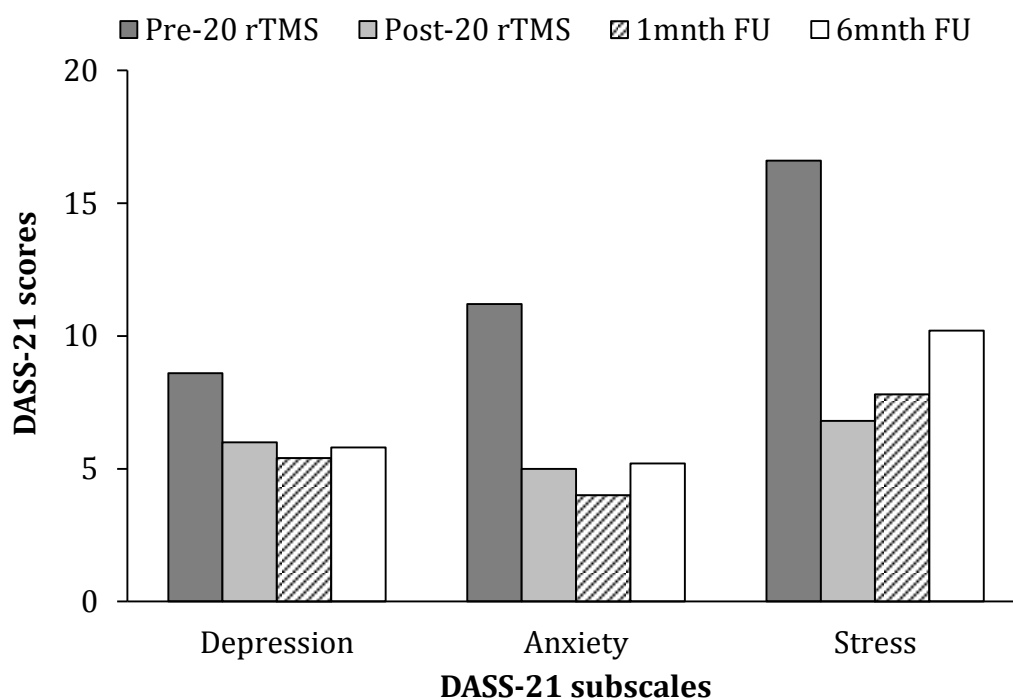


Figure 5.8 Mean DASS-21 subscale scores pre and post the 20 rTMS sessions and at 1 and 6 month follow-up

DASS-21: 21-item depression, anxiety and stress scale; mnth: month; FU: follow-up

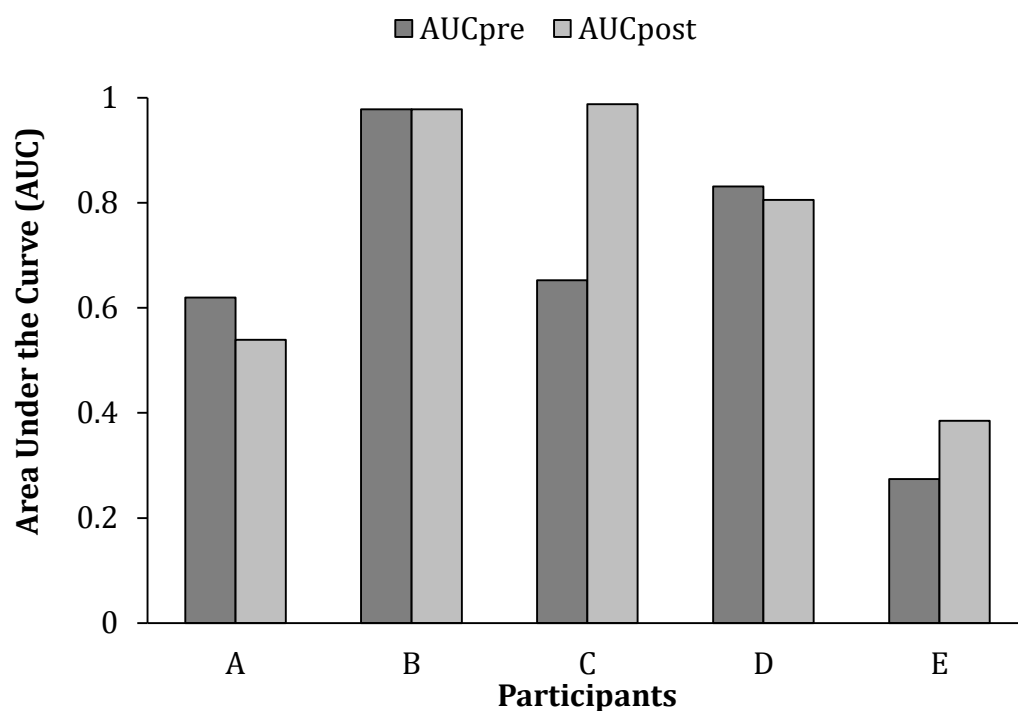


Figure 5.9 Area under the curve pre and post the 20 rTMS sessions for each participant.

Greater AUC indicates reduced TD, i.e. preference for larger, delayed rewards.

Qualitative results

From participants

The most unanimous feedback from patients regarding the benefits of rTMS related to feeling calmer, less anxious, improvements in mood and a general increase in their hopes and motivation towards recovery. Participants reported feeling “better equipped to cope with things”, “calmer [and] having a brighter mood” and that “my improved mood helped me manage my life, specifically my anorexia, far better.” Improvements in self-esteem were also reported “I generally feel better and happier in myself on a daily basis” along with decision making abilities, being able to rationalise things, in particular in relation to new/changes in treatment plans, and a broader optimism that these small changes could lead to “bigger and better things”.

In relation to ED symptoms specifically, almost all participants said they felt little to no changes during the four weeks that the 20 sessions were

administered, however a few weeks after completion was when most participants reported feeling noticeable differences. Participants reported feeling better able to manage food related difficulties, “[rTMS has] enabled me to tackle my anorexic habits more successfully” and that they felt more optimistic “I feel more hopeful and less despair in relation to my illness.” Whilst some participants said they noticed no change to the frequency of their binge/purge behaviours, others reported that “I make myself sick far, far less” as a result of feeling “less motivated to engage in purging behaviours” describing them as “less rewarding.” Additionally, one participant noticed a reduction in mirror checking behaviours along with improved sleep (previously getting 4 hours per night which increased to over 8 hours per night following the rTMS).

Whilst most participants seemed to agree that although the “difference [rTMS makes] is small... that this was “...hugely significant”. Almost all participants implied that it had done more for them than any other form of treatment they had tried – “it is the first therapy that has had any impact on me” and all participants have expressed interest in having more sessions.

From carers, partners, parents or friends

Similarly to what was reported by participants, the main feedback from carers and loved ones suggested notable “improvements in mood” along with improvements in coping abilities and individuals being more “logical, rational, less resistant to change and thinking more clearly”. Likewise, changes to participants self-esteem and general demeanour was noted as they were “more confident, bolder and adventurous” or “more relaxed and smiley”. In general, “a more positive and energised outlook on life” was reported by most carers/loved ones.

In relation to ED specific symptoms and behaviours, little to modest improvements in were reported. As all participants were adults who typically lived independently and therefore ate alone/unsupervised (with the exception of the inpatient, Participant A) eating behaviours were difficult for others to comment on. However, “periods of normal eating” and more relaxed approaches

to foods, for example “trying new foods... outside of her routine or food type” were reported. Furthermore some feedback suggested a reduction in purging behaviours, and increased “motivation and determination” towards recovery. A number of carers/loved ones suggested that they thought the participants expressed desire for more rTMS sessions reflected them “feeling the benefit of rTMS”.

Discussion

Following approximately 20 sessions of neuronavigated rTMS in five cases of treatment-resistant and enduring AN, improvements in ED symptoms and general psychopathology were reported. Moreover, these improvements were sustained or even continued to improve for up to 6 months following treatment. However, these improvements in psychopathology were not associated with weight gain. The rTMS intervention was well accepted and both participants and carers reported positive feedback regarding the treatment. There were no general trends in the effects of rTMS on TD behaviour, however one individual demonstrated a substantial reduction in TD and thus an increase in the ability to delay gratification.

It is important to highlight and consider the illness history and treatment resistant nature of the participants involved. The average duration of AN was over 20 years and all had failed other forms of psychological, pharmacological and/or neuromodulatory (ECT) therapy. Whilst some individuals were receiving concurrent psychological or pharmacological treatment, they had done so for a long time prior to starting the rTMS, with limited response. Prior resistance to pharmacotherapy in depression reportedly diminishes the likelihood of responding to subsequent interventions, including neuromodulation (Prudic et al., 1996; Sackeim et al., 2001). Similarly, resistance to previous treatment in AN is likely to predict poor outcomes in future interventions. Given this and the chronic, enduring nature of the five cases discussed, we believe a placebo response is unlikely and that the symptom improvements seen are, at least in part, a result of the rTMS treatment. This point is further emphasised by the maintenance and even continued

improvement in both ED specific and general psychopathology at up to 6 months following the intervention. Moreover, we expected that given the severity and enduring nature of AN in these individuals, additional sessions, more intense rTMS protocols, concurrent psychotherapy and/or longer follow-ups may be required in order to encourage weight gain.

Potential mechanisms of therapeutic effect

A number of potential mechanisms may explain the therapeutic effects of rTMS seen within these five AN cases. Improvements in symptoms and general psychopathology may be due to direct, focal modulation of the DLPFC and dorsal neural circuitry responsible for executive functions and mood regulation. In particular rTMS to the left DLPFC may alter the self-regulation difficulties seen in AN, i.e. by improving control over compulsive ED related behaviours/symptoms. However, this was not reflected across all individuals in the TD task. Alternatively, whilst the neural effects of rTMS are often thought to remain relatively focal, recent evidence suggests that rTMS to the PFC induces remote effects in deeper, thalamic structures (George et al., 1999). Therefore, neural modulation of the DLPFC with rTMS within this study may have remotely altered ventral circuitry, altering bottom up, mesolimbic emotional drives related to AN specific stimuli such as food and eating situations.

Both the dorsal and ventral circuitry involved in AN may be altered with rTMS via a number of biological pathways. Firstly, given the argued neuro-circuit nature of intractable AN, the observed changes to some of the inherent and 'stubborn' aspects of the illness may be a result of rTMS induced changes to neuroplasticity (Gersner et al., 2011; Medina & Tunez, 2013; Ridding & Rothwell, 2007). In particular, HF rTMS is proposed to facilitate LTP like changes in structural and functional synaptic connections, producing effects that outlast the stimulation period and thus underlying therapeutic effects (Esslinger et al., 2014; Vlachos et al., 2012). Whilst glutamate plays a central role in this process, BDNF is essential for synaptic regulation and plasticity. In treatment resistant depression, BDNF is inversely correlated with illness severity and a biomarker of response to rTMS (Fidalgo et al., 2014). Moreover,

levels of BDNF are increased following HF rTMS, suggesting a normalising effect of rTMS treatment (Gersner et al., 2011; Zanardini et al., 2006). This is particularly pertinent to AN, given the abnormalities in BDNF levels reported across different stages of the illness (Brandys et al., 2011; Zwipp et al., 2014). Therefore, as in other neuro-circuit based psychiatric disorders such as depression, rTMS is likely to induce neuroplasticity via the modulation of BDNF expression.

Secondly, rTMS has demonstrated the ability to alter levels of monoamine neurotransmitters. Modulation of dopamine release in remote areas such as the anterior cingulate cortex, has been reported following HF rTMS to the left (but not right) DLPFC (Cho & Strafella, 2009). Given these and other similar findings (Pogarell et al., 2007), in conjunction with the dopaminergic alterations reported within AN (Frank et al., 2005), this focal and remote normalisation of dopamine may underlie the therapeutic effects reported within these five participants. Additionally, modulation of serotonin following HF rTMS to the PFC has been reported (Baeken et al., 2011; Kanno et al., 2003) and may also contribute to the therapeutic effects of rTMS in AN.

Finally, the combination of rTMS and cue exposure included within the current protocol may have bolstered the reduction in ED related anxieties experienced by participants. Evidence supports the importance of context-dependent neural activity on outcome of rTMS. For example, HF rTMS increased levels of BDNF and glutamate in awake, alert animals. However, in anaesthetised animals, levels of these neuroplasticity markers were reduced (Gersner et al., 2011). Therefore, the therapeutic efficacy of rTMS in AN reported here might not have been achieved with either rTMS or exposure therapy alone.

Strengths

Until now, evidence for the potential therapeutic benefit of rTMS in AN has been limited to one other case report (Kamolz et al., 2008) and our small, uncontrolled pilot study demonstrating short-term effects of rTMS on AN symptoms (Van den Eynde, Guillaume, et al., 2013). The RCT outlined in Chapter 3, along with the five cases reported here, add to this sparse literature by

providing further evidence for the feasibility, acceptability and some suggestion of therapeutic efficacy of rTMS in severe AN.

Furthermore, the rTMS investigations reported within this thesis are the first within AN to use improved rTMS methodologies such as evaluating MT via EMG recordings (rather than the observed method) and using MRI-guided technology/neuronavigation (rather than the 5-cm anterior, scalp measurement method). This is a significant improvement to previous rTMS protocols as these techniques allow for more accurate, safer and reliable administration of rTMS, which is particularly important in repeated, therapeutic protocols.

Limitations

The lack of weight gain, and in fact slight weight loss at follow-up, cannot be ignored as weight gain is an obvious treatment goal in this group. However, the natural history of enduring AN across cases demonstrates that changes in weight require both time, and significant improvements to participants' psychological state. Most participants reported noticeable changes to factors such as motivation, coping ability and affect regulation during or after the course of rTMS sessions – therefore, perhaps with time and concurrent psychotherapy these improvements could be utilized to encourage weight gain. A number of participants suggested that they thought psychotherapy alongside the rTMS intervention would be useful, in order to take full advantage of the psychological improvements they felt during/following the rTMS.

The effectiveness of the food exposure videos used within this study is somewhat compromised by their lack of salience (within the food challenge task reported in Chapter 3). Moreover, the fact that participants watched these videos twice during each session, totalling 40 times, undoubtedly diminishes their potency in arousing AN related experiences. Furthermore, these videos depict other people eating highly palatable foods and are therefore seen by participants from a third person perspective. Given these considerations, our group has now developed a larger variety of new, food-centric videos, which aim to elicit stronger, temporary, ED related experiences for use alongside neuromodulation techniques. Similarly, as discussed in Chapter 4, the TD task

used within this thesis is limited. However, Chapter 4 demonstrated that compared to sham, real rTMS lead to short-term reductions in TD. Therefore this task might not be appropriate to assess changes in intertemporal choice behaviour over a longer duration/exposure to rTMS. Moreover, whether or not this construct can be permanently altered with rTMS (Figner et al., 2010) or rather, is a stable personality trait (Davis et al., 2010) requires further clarification.

Whilst this study was intended to be an exploratory, feasibility case series the small sample size and lack of control condition is a limitation of this research and should therefore be considered when interpreting and generalising the findings. Whilst larger, controlled studies are needed to confirm our results, this study provides preliminary evidence for the therapeutic efficacy of rTMS in severe and enduring AN.

Future directions

As a next step, larger case study trials of therapeutic rTMS in AN are warranted, in order to explore its suitability for different target populations (e.g. restricting or binge-purge type AN) or target symptoms (e.g. ED symptoms or symptoms of comorbid disorders, such as severe depression, OCD or post-traumatic stress disorder, that are known to respond to rTMS treatment). In the longer term, large scale high quality RCT of therapeutic rTMS in participants with AN are needed together with research into different rTMS protocols for AN and for ED in general, utilising different types of stimulation (high or low frequencies, uni- or bilateral, or different stimulation sites). Such research will help to further clarify the neuro-circuitry underpinning of different symptoms, in addition to establishing the therapeutic potential of neuromodulation techniques in treating ED. Such tools, if proved beneficial, could exist as viable adjuncts to existing psychotherapy interventions.

Conclusions

Despite the small, case series style of this study, these findings provide further, albeit preliminary evidence for the therapeutic efficacy of rTMS in AN. The

therapeutic benefits on ED psychopathology and mood were maintained or continued to improve for up to six months. Of note, the five individuals studied had particularly enduring AN of a treatment-resistant nature, which may explain the lack of weight gain seen within this study. Further research is needed in larger samples, with control conditions and alongside neuroimaging modalities, in order to elucidate the neural mechanisms that underlie the reported therapeutic effect of rTMS in AN.

Chapter 6. General overview

Hypotheses tested

Four major hypotheses were tested in this thesis:

Hypothesis 1. Existing literature demonstrates that in human and animal populations, neuromodulation techniques have the ability to alter feeding and eating behaviour, body weight and ED related symptoms, and therefore have potential in the treatment of ED.

Hypothesis 2. In patients with AN, core symptoms of AN will be reduced immediately and 24 hours after a single-session of real (as opposed to sham/placebo) HF rTMS to the left DLPFC.

Hypothesis 3. Excessive cognitive control in AN will be reduced following real (as opposed to sham) HF rTMS to the left DLPFC.

Hypothesis 4. In patients with enduring AN, ED and related psychopathology (e.g. mood) and weight will be improved immediately following therapeutic (20 sessions) HF rTMS to the left DLPFC and at follow-up, up to 6 months later.

Summary of findings

The first hypothesis was tested in a systematic review of the literature on the effects of neuromodulation on feeding and eating related outcomes and body weight in animals and humans (healthy individuals, those with ED or other neurological/psychiatric conditions) (Chapter 2). The non-invasive techniques, rTMS and tDCS, when applied to the PFC, demonstrate potential in reducing food cravings. rTMS to the left DLPFC and the DMPFC has been shown to improve symptoms of BN. Improvements in AN symptomatology and weight gain have been reported following both rTMS to the left DLPFC and DBS to a variety of targets including the subgenual cingulate cortex, ventral striatum and nucleus accumbens. Also, DBS to areas such as the sub-thalamic nucleus and globus pallidus has been associated with weight gain in other disorders (e.g. Parkinson's) and DBS to the lateral hypothalamus has been shown to increase food intake/body weight in animals – i.e. providing further support for its potential in AN. VNS has been associated with weight loss in obese people,

individuals with depression and epilepsy, and has consistently been shown to reduce food intake/body weight in animals. Despite some limitations in the ability to generalise from these findings, the systematic review supports the conduct of further research into the utility of neuromodulation treatment in ED and obesity.

Hypotheses 2 and 3 were tested in a single-session, double blind RCT of real versus sham neuronavigated HF rTMS to the left DLPFC in patients with AN (Chapter 3 and 4). Compared to sham treatment, individuals who received real rTMS reported reduced levels of core AN symptoms, which is consistent with our earlier findings (Van den Eynde, Guillaume, et al., 2013). However, across most measures of psychopathology, there was also an indication of placebo effects (Chapter 3.3). Real rTMS increased the liking of specific foods (sweet biscuits) whilst sham decreased it; however, this was not associated with any changes in food intake (Chapter 3.4). Unlike findings from studies of other psychiatric disorders, including BN (Claudino et al., 2011), salivary cortisol concentrations were not altered following rTMS in AN (Chapter 3.5). In contrast to another report (Khedr, El Fetoh, et al., 2014), the AN participants in the present study demonstrated reduced levels of cortical excitability and these were associated with worse symptomatology (Chapter 3.6). Finally, this study provides further evidence that rTMS is a safe, well-tolerated and acceptable form of treatment in AN (Chapter 3.7). Whilst the present RCT was underpowered, it provides proof-of-principle of the therapeutic potential of rTMS in AN.

Since rTMS has been shown to improve symptoms in AN, we aimed to assess whether these effects were underpinned by the ability of rTMS to reduce excessive cognitive control (Figner et al., 2010) proposed to be involved in AN (Steinglass et al., 2012). Compared to sham, real rTMS reduced the discounting of future monetary rewards, i.e. encouraged more prudent decision making (Chapter 4). These findings were the opposite of what was hypothesised. They suggest that the effects of rTMS on symptoms of AN may rely on its ability to improve control over AN symptoms/behaviours rather than reducing excessive 'self-control' specifically.

Hypothesis 4 concerning the therapeutic utility of rTMS in AN was tested in a case series of five patients with enduring AN (Chapter 5). Following 20 daily sessions of neuronavigated rTMS, improvements in ED and general psychopathology were found and these were sustained for at least 6 months. However, these improvements were not associated with weight gain. The chronicity, severity and treatment-resistance of participants' illness are likely to have accounted for the lack of rTMS effects on weight gain. At the same time it probably also diminished the possibility of a placebo response in these individuals and suggests that despite the unblinded, open-label nature of the intervention, effects on ED symptoms and general psychopathology were 'real'.

Strengths

The main strengths of the research are the improved and novel methodologies employed. Unlike other studies in ED, it used more accurate methods of delivering rTMS. This included studying MEP to estimate MT: this is argued to be more accurate, conservative and safer than previously employed methods (Rossi et al., 2009). Moreover, all rTMS was delivered using neuronavigation and therefore is expected to have stimulated the left DLPFC more accurately and effectively than studies that used the 5cm anterior DLPFC location method (Fitzgerald et al., 2009). Finally, this research examined novel aspects of the effects of neuromodulation in ED that have not previously been considered. For example, the study examined how rTMS alters hedonic drives such as the liking of food in AN. It also investigated cortical excitability. It is the first research in ED to report changes on a neuropsychological outcome, intertemporal choice, following rTMS. These elements all improve methodology and underlying theory and pave the way for future research.

Limitations

Sample

The inclusion criteria for participants to take part in the research reported in this thesis were narrow and therefore limit the generalisability of findings. For example, the minimum BMI requirement was adopted for safety reasons

however, this reduces the ability to extrapolate findings to individuals with AN who are severely underweight.

The participants had enduring forms of AN and had an average illness duration of over 10 years. This may reflect the type of individual willing to engage in the study; i.e. it is likely that individuals who are interested in participating in research on alternative and novel approaches to AN (such as rTMS) have had unsuccessful attempts at other, more conventional treatments. This compromises the generalisability of the findings to less severe/less chronic forms of AN. However, as rTMS is recommended as a second-line treatment for depression (Gaynes et al., 2014) it is likely that, if proved efficacious, this would also be the case for AN, i.e. it would not be used before some type of 'talking' therapy was attempted.

Given the instability and diagnostic flux in ED (Milos et al., 2005), phenotypical and diagnostic considerations are important. Moreover, symptomatology such as binge-eating and dietary restraint have been proposed to arise from different neural mechanisms (Brooks et al., 2012). With regards to AN, the effects of neuromodulation on specific symptoms may be more effectively evaluated via research on isolated AN subtypes, or alternatively, studies that are adequately powered to compare effects within and between subtypes. This point is demonstrated in the current research, as the AN subtypes differed in symptom severity.

Methodology

Although a double-blind RCT design was employed, i.e. both participants and researchers (who administered the pre/post rTMS measures) were unaware of intervention allocation, it was not feasible for the researcher applying rTMS to be blinded. As participant blinding was only partially successful it is possible that implicit cues may have impacted upon blinding success. This point is emphasised by the data, which suggest that participants were surer than researchers (who were out of the room during rTMS procedures) as to which intervention they had. Also, a lot of individuals were recruited from the same outpatient department; therefore communication between participants about the study

may have impacted both the primary outcomes and blinding success of this research. Moreover, real rTMS was reported as significantly more uncomfortable than sham and this is likely to have impacted the ability to correctly guess stimulation type. The inability of current sham techniques to adequately mimic real rTMS is a methodological limitation in rTMS research.

The randomisation procedure was stratified by AN diagnoses. However, compared to the sham group, those in the real rTMS group had reduced initial rates of psychopathology. This was by chance and is likely to be a reflection of the increased proportion of binge/purge subtypes in the sham group who (as a group) reported worse symptomatology. Whilst these differences between real/sham groups were not significant immediately prior to rTMS, they must be considered when interpreting the findings. Moreover, this supports the case for studying AN subtypes independently, given their characteristic differences in symptomatology.

A recent study utilising multiple measures reported heightened excitability in AN, one of which was resting MT (Khedr, El Fetoh, et al., 2014). The present study is limited to this single measure of cortical excitability and reports reduced rates compared to those reported by Khedr, El Fetoh, et al. (2014) and this was associated with worse symptomatology (i.e. lower BMI and increased EDE-Q scores). No other study on the effects of rTMS on ED symptoms has reported this measure. In addition to providing information on cortical activity in ED, it is also an important safety consideration with regards to the increased susceptibility/risk of seizure.

This research lacked a HC comparison group, which would have been particularly useful in regards to both cortical excitability and rates of TD. Moreover, our TD task did not differentiate the way in which it frames reward choices and this may have hampered its ability to thoroughly capture discounting behaviour in AN. For example, unlike Steinglass et al. (2012), we did not observe differences in TD between AN subtypes.

Implications of this research

This study demonstrates the potential of neuromodulatory tools in improving ED related symptoms. Specifically, compared to sham, a single-session of real rTMS was shown to lead to reduced AN symptoms and it also demonstrated long-term, therapeutic potential. Moreover, real rTMS altered intertemporal choice behaviour in AN – increasing prudent, controlled choices – which may act as a neuropsychological marker of response to rTMS in AN.

The present findings suggest that rTMS alters the neurocircuitry associated with AN, especially those that contribute to difficulties in self-regulatory control. Neuroplasticity may play a role in these therapeutic effects (Gersner et al., 2011). Specifically, modulation of BDNF (Fidalgo et al., 2014; Zanardini et al., 2006) along with alterations in the concentration of the neurotransmitters dopamine (Cho et al., 2014; Cho & Strafella, 2009) and serotonin (Baeken et al., 2011) have been reported following rTMS in depression. Given reported alterations in the levels of these substances in AN (Brandys et al., 2011; Phillipou et al., 2014), their modulation via rTMS may contribute to effects on symptomatology.

Excessive cognitive control is often proposed to underlie AN, manifesting in ‘self-controlled’ behaviours such as dietary restraint (Kaye et al., 2009; Steinglass et al., 2012). Preliminary data suggest that prudent decision making is reduced following rTMS in healthy people (Figner et al., 2010) and therefore we proposed that this might underlie the therapeutic effects of rTMS in AN. However, the results of the present research suggest that activating the PFC promotes controlled decision making in AN, whilst also improving symptoms. Therefore, the concept of ‘excessive cognitive control’ and its effects on symptoms in AN is questionable. Rather, it is possible that individuals with AN may lack control over what are typically perceived as ‘self-controlled’ symptoms, such as dietary restraint. Therefore, rTMS may alter the neurocircuitry underlying self-regulatory control difficulties and subsequently improve control over compulsive, ED habitual symptoms/behaviours. This is schematically presented in Figure 6.1; an AN-specific amendment of the diagram described in Chapter 1 that incorporates findings from the present research. Specifically, the altered

neurocircuitry hypothesised to be present in AN may not lead to extreme self-control per se, but to an impaired ability to control ED behaviours such as food restriction and levels of feeling full/fat. Activating the DLPFC with rTMS may alter activity in this and related areas, resulting in improvements in self-regulatory control mechanisms over ingrained and compulsive symptoms of AN.

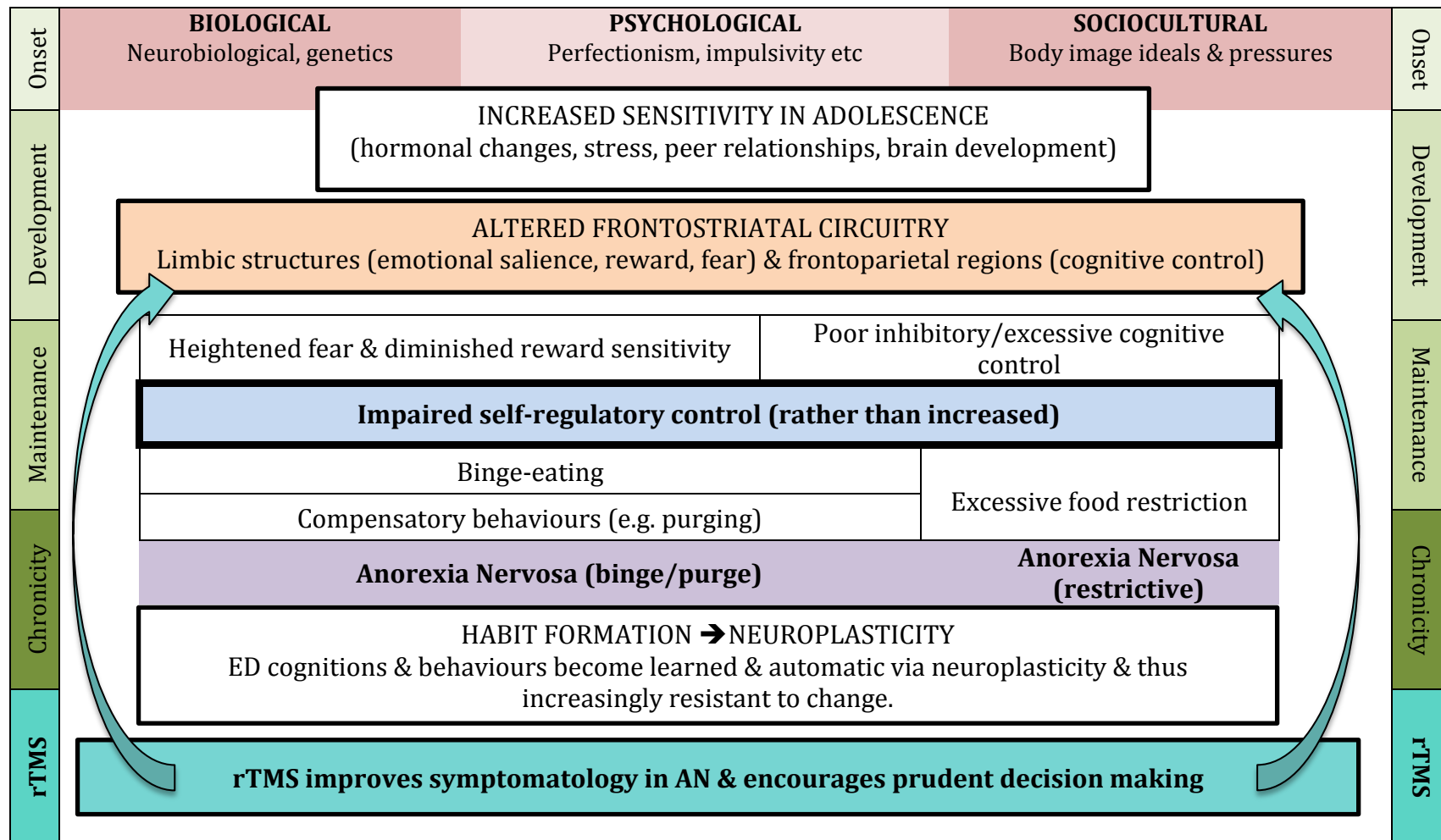


Figure 6.1 An amended version of the figure presented in Chapter 1 that incorporates the findings from this research.

Directions for future research and clinical implications

Repetitive transcranial magnetic stimulation in anorexia nervosa

The proof-of-principle of rTMS as a potential adjunct to treatment in AN was demonstrated in the RCT and in the small uncontrolled case series. However, before rTMS is considered as either a stand-alone or adjunctive treatment option for adults with AN, these preliminary findings need to be consolidated, extended and replicated. For example, the superior short-term efficacy of real (as opposed to sham) rTMS in reducing AN symptoms reported here needs to be replicated. In addition, a sham-controlled therapeutic RCT of rTMS in AN would shed more definitive light on its therapeutic efficacy and clinical value.

Future research on rTMS in AN needs to determine optimal stimulation protocols. For example, the importance of using excitatory (HF)/inhibitory (LF) rTMS, the role of hemispheric lateralisation and optimal targets remain undefined. Moreover, therapeutic trials with pre- and post-neuroimaging assessments would probe neural models of AN and enable an exploration of possible biomarkers of response to rTMS in AN, along with providing a clearer understanding of rTMS induced neural changes in AN. Finally, whether or not rTMS is optimal as a stand-alone or as an adjunct to other treatments needs to be established, as does the efficacy of rTMS in different types (binge/purge and restrictive) and stages (early/enduring and treatment resistant) of AN.

Temporal discounting in eating disorders

Differences in TD across the spectrum of ED, and the association of TD with ED symptomatology are poorly understood. Data are limited to a small number of studies in obesity, BED and AN. Therefore, future studies are needed that compare TD across the spectrum of ED to elucidate whether this construct is sensitive to diagnostic and symptom differences in ED. Similarly, the neural correlates of TD require further clarification as well as the effects of neuromodulation on TD behaviour. Further research is needed in order to understand the utility of TD tasks in relation to ED and the neural correlates of intertemporal choice in order to develop tailored neuromodulation protocols.

Neuromodulation in eating disorders

Other than rTMS, there is a range of established and emerging neuromodulatory techniques. Within each lie a variety of protocol parameters – e.g. excitatory/inhibitory effects, increased depth/strength of stimulation etc. Given this, there is an increased need to refine brain-directed interventions for specific diagnoses and symptomatology in ED. Future research should be based on neuroimaging data. Thus, a clearer understanding of the role of specific brain structures and their connectivity with other key regions will contribute to the refinement and optimisation of neuromodulation protocols. Moreover, combined neuroimaging and neuromodulation protocols are needed to probe disease mechanisms and identify biomarkers of response (Fidalgo et al., 2014; Grefkes & Fink, 2009).

Ethical and clinical considerations

Ethical considerations regarding to the use of neuromodulation as treatments for ED must go beyond efficacy and safety (Synofzik & Schlaepfer, 2010). Although individuals with AN are open and positive about brain-directed treatments, questions remain regarding respect for autonomy i.e. the ability for informed consent, authenticity/agency i.e. self-perception and understanding the role of the self within the illness, and self-efficacy (Coman, 2014; Coman, Skarderud, Reas, & Hofmann, 2014).

Whilst such ethical debates and the research reported in this thesis suggest that rTMS is viewed as an acceptable form of treatment by individuals with AN, earlier generations of brain-directed treatments (such as ECT or surgical interventions e.g. lobotomy) for psychiatric illnesses have been controversial because of serious side-effects and their irreversible nature (Synofzik & Schlaepfer, 2010). In order to progress research, it is important to further establish patients, carers and clinician's views on the use of neuromodulation in ED. Resources/discussions which provide easily understandable information regarding the rationale behind the use of neuromodulation in ED may help to bridge the gap between scientists and clinicians/patients and thus encourage more high-quality research into the clinical utility of neuromodulation in ED.

Conclusions

In this thesis I have reviewed the field of ED and proposed neurocircuit based aetiological models, which highlight the need for brain-directed interventions. The systematic review of the effects of neuromodulation on ED related outcomes supports the empirical nature of this thesis. The RCT demonstrates that compared to sham, real rTMS leads to reduced AN symptoms, alters food preferences, does not alter biological stress responses, provides a valid and useful measure of cortical excitability and is safe, tolerable and acceptable in AN. Additionally, real rTMS alters intertemporal choice behaviour, which may imply that rTMS leads to increased control over symptoms in AN. Finally, the data regarding five cases of enduring AN suggest that rTMS induces sustained improvements in ED and general psychopathology. As a whole, this thesis adds to the growing evidence supporting the need and utility of brain-directed interventions for ED.

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Appendix A: Published papers associated with this thesis

Appendix A.1 Systematic review (Chapter 2)

REVIEW

A Systematic Review of the Effects of Neuromodulation on Eating and Body Weight: Evidence from Human and Animal Studies

Jessica McClelland*, Natali Bozhilova, Iain Campbell & Ulrike Schmidt

Section of Eating Disorders, Institute of Psychiatry, King's College London, London, UK

Abstract

Background: Eating disorders (ED) are chronic and sometimes deadly illnesses. Existing treatments have limited proven efficacy, especially in the case of adults with anorexia nervosa (AN). Emerging neural models of ED provide a rationale for more targeted, brain-directed interventions.

Aims: This systematic review has examined the effects of neuromodulation techniques on eating behaviours and body weight and assessed their potential for therapeutic use in ED.

Method: All articles in PubMed, PsychInfo and Web of Knowledge were considered and screened against a *priori* inclusion/exclusion criteria. The effects of repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation, vagus nerve stimulation (VNS) and deep brain stimulation (DBS) were examined across studies in ED samples, other psychiatric and neurological disorders, and animal models.

Results: Sixty studies were identified. There is evidence for ED symptom reduction following rTMS and DBS in both AN and bulimia nervosa. Findings from studies of other psychiatric and neurological disorders and from animal studies demonstrate that increases in food intake and body weight can be achieved following DBS and that VNS has potential value as a means of controlling eating and inducing weight loss.

Conclusions: Neuromodulation tools have potential for reducing ED symptomatology and related behaviours, and for altering food intake and body weight. In response to such findings, and emerging neural models of ED, treatment approaches are highly unlikely to remain 'brainless'. More research is required to evaluate the potential of neuromodulation procedures for improving long-term outcomes in ED. Copyright © 2013 John Wiley & Sons, Ltd and Eating Disorders Association.

Keywords

eating disorders (ED); anorexia nervosa (AN); bulimia nervosa (BN); transcranial magnetic stimulation (TMS); transcranial direct current stimulation (tDCS); vagus nerve stimulation (VNS); deep brain stimulation (DBS)

***Correspondence**

Jessica McClelland, BSc, P059, Section of Eating Disorders, Institute of Psychiatry, King's College London, De Crespigny Park, London SE8 8AF, UK. Tel: +44207 848 0183. Email: jessica.mcclelland@kcl.ac.uk

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Introduction

Eating disorders

The eating disorders (ED) anorexia nervosa (AN), bulimia nervosa (BN), eating disorders not otherwise specified (EDNOS) and binge eating disorder (BED) are characterised by pathological eating behaviours and body image disturbance. Obesity is a heterogeneous condition that is not classified as an ED (Marcus & Wildes, 2009). However, it is both a risk factor and a consequence of ED. Moreover, a subgroup of obese people has significantly altered eating behaviour (e.g. loss of control over eating), and the combination of ED and obesity is increasing (Darby et al., 2009).

In the past decade, there has been an increase in studies of the neural underpinnings to ED. A number of systematic reviews have assessed the literature on structural imaging in ED (Van den Eynde et al., 2012) and functional neuroimaging with and without symptom provocation in AN patients (Pietrini et al., 2011; Zhu et al., 2012). In addition, there are narrative reviews on the use

of neuroimaging techniques in ED (Frank, Bailer, Henry, Wagner, & Kaye, 2004; Frank & Kaye, 2012; Kaye, 2008; Kaye, Fudge, & Paulus, 2009; Kaye, Wagner, Fudge, & Paulus, 2011; Michaelides, Thanos, Volkow, & Wang, 2012). Whilst these reviews summarise findings from a variety of neuroimaging techniques including positron emission tomography and single photon emission computed tomography, the most extensive imaging data in ED arise from fMRI research.

Functional MRI has advanced our understanding of the neural differences between people with ED and their healthy counterparts. Altered activity in the insula (Kim, Ku, Lee, Lee, & Jung, 2012) and abnormalities in the processing of rewards (Avena & Bocarsly, 2012; Bohon & Stice, 2011; Brooks et al., 2011; Dichter, Damiano, & Allen, 2012; Holsen et al., 2012; Stice, Spoor, Bohon, Veldhuizen, & Small, 2008) in addition to alterations in frontal regions have been reported (Brooks et al., 2011; Celone, Thompson-Brenner, Ross, Pratt, & Stern, 2011; Hollmann et al., 2012; Marsh et al., 2011; Uher et al., 2004), and subsequent neural models of ED have been developed (Brooks, Rask-Andersen,

Benedict, & Schioth, 2012; Kidd & Steinglass, 2012; Marsh, Steinglass, *et al.*, 2009; Steinglass & Walsh, 2006).

Many of the brain regions that are proposed to be involved in the aetiology/symptomatology of ED involve parts of the ventral and dorsal circuits proposed in emotion regulation models. For example, Phillips, Drevets, Rauch, and Lane (2003) proposed that a ventral/limbic circuit is central to the identification of and response to emotional salient stimuli, whilst a dorsal or cognitive/executive functioning circuit is important for automatic regulation of emotional responses, selective attention and planning. This and other models of emotion regulation propose that there is 'bottom-up' emotion generation arising from subcortical, limbic neural structures and 'top-down' regulation by dorsal prefrontal cortical regions (Ochsner & Gross, 2007; Phillips *et al.*, 2003). There is a growing consensus that ED may, at least in part, be explained by altered interactions within such circuitry (Kaye *et al.*, 2009, 2011; Marsh, Maia, & Peterson, 2009; van Kuyck *et al.*, 2009). Heightened 'bottom-up' mesolimbic drives may contribute to altered reward processing, for example in relation to food stimuli, and result in behaviours such as binge eating, whilst overactive 'top-down' processes involving the dorsal circuit may lead to excessive regulation and self-control, thus contributing to behaviours such as food restriction.

Despite the growing body of neuroimaging data and the emergence of neural models of ED, there is a lack of targeted treatment interventions. At present, the leading treatment for AN in adolescents is family based therapy (FBT); yet, there is still no 'gold standard' treatment for adult AN (Watson *et al.*, 2012; Schmidt *et al.*, 2012). In BN and BED, cognitive behaviour therapy (CBT) is considered the treatment of choice for adults and adolescents; yet, recovery rates are far from perfect (Brown & Keel, 2012; Schmidt *et al.*, 2007). Drop-out and relapse rates in treatments for ED are high (Dejong, Broadbent, & Schmidt, 2012; Schmidt *et al.*, 2012). Whilst existing treatments work for some, a significant number of individuals do not respond to any of the treatment options currently available.

Existing talking psychotherapies target explicit cognitive processes. They work by teaching patients to employ effortful and conscious strategies to divert attention from anxiety-provoking thoughts. There is an indubitable need for such approaches within the field. However, we suggest that on the basis of the neuroimaging research summarised herein, there is also a need for brain-directed approaches to be used as adjuncts to current interventions in order to improve outcomes. Whilst drug therapies are a form of brain-directed treatment, their value in ED is currently limited (Mitchell, Roerig, & Steffen, 2013) (however, see Maguire *et al.*, this issue). Therefore, there is significant scope for investigations into techniques that have the ability to

directly, focally and implicitly influence the subcortical processes proposed to underlie ED.

Neuromodulation

Neuromodulation procedures are emerging as techniques that can be used to stimulate or inhibit neural activity. Techniques range from relatively non-invasive procedures, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), to more invasive procedures requiring surgery, such as vagus nerve stimulation (VNS) and deep brain stimulation (DBS). Such techniques are advantageous compared with older brain-directed treatment approaches, such as electroconvulsive therapy (ECT), as they are non-lesional, adjustable and without severe side effects. Those investigated most widely and relevant to the current review are summarised in Table 1.

Two forms of non-invasive neuromodulatory techniques are TMS and tDCS. Primarily developed in order to investigate motor cortex excitability, TMS modulates the underlying cerebral cortex and neural activity beneath the site of stimulation via an electromagnetic field generated by a coil (Barker, Jalinous, & Freeston, 1985). Delivery of single pulse TMS enables examination of cortical excitability, whilst the delivery of multiple pulses over a short period, known as repetitive TMS (rTMS), induces longer lasting neural effects. When applied at a low frequency (<5 Hz), rTMS suppresses cortical excitability, whilst high-frequency rTMS (>5 Hz) enhances cortical excitability. Recent evidence suggests that high-frequency rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) has therapeutic efficacy in depression (Berlim, Van den Eynde, & Daskalakis, 2012; Fitzgerald *et al.*, 2012; Lee, Blumberger, Fitzgerald, Daskalakis, & Levinson, 2012; O'Reardon *et al.*, 2007; Tarhan, Sayar, Tan, & Kagan, 2012). As such, rTMS is approved by the FDA in the USA as a second-line treatment for depression.

Transcranial direct current stimulation applies a weak direct current from one electrode (excitatory; anode) to another (inhibitory; cathode). In comparison with rTMS, the mechanism by which tDCS works enables multiple stimulation designs. Switching the position of the electrodes enables swapping of excitation/inhibition between the right and left hemispheres. Despite this added feature and that in comparison with rTMS, it is safer, cheaper and easier to administer, tDCS has not been as widely investigated. However, interest in tDCS is increasing, having shown promising therapeutic effects in both Parkinson's disease (Benninger *et al.*, 2010; Boggio *et al.*, 2006; Fregni *et al.*, 2006) and Alzheimer's disease (Ferrucci *et al.*, 2008) and, more recently, in major depression (Ferrucci *et al.*, 2009; Kalu, Sexton, Loo, & Ebmeier, 2012; Loo *et al.*, 2012; Nitsche, Boggio, Fregni, & Pascual-Leone, 2009).

Table 1 Common neuromodulation techniques

Type	Invasiveness	Mechanism of action
Transcranial magnetic stimulation (TMS)	Non-invasive	Electromagnetic induction leads to modulation of underlying cortex and neural activity.
Transcranial direct current stimulation (tDCS)	Non-invasive	Weak current alters neuronal excitability. Neural effects depend on the direction of current.
Vagus nerve stimulation (VNS)	Surgery	Electrical stimulation of vagus nerve conveyed to other areas of the brain.
Deep brain stimulation (DBS)	Surgery	Electrical pulses delivered to specific brain area central to condition.

Some forms of neuromodulation are more invasive and require surgical procedures. VNS involves the implantation of a stimulator device; the generator is placed under the clavicle in the chest and is connected to electrodes wrapped around the vagus nerve (Connor, Nixon, Nanda, & Guthikonda, 2012; Meneses et al., 2013). The vagus nerve, one of 12 cranial nerves, relays information to and from the brain to major organs including the heart, stomach and lungs. Electrical stimulation via VNS results in activation/inhibition of brainstem structures, which is then conveyed to other areas of the brain including the thalamus, frontal cortex, hypothalamus and limbic lobe (Chae et al., 2003). VNS is FDA approved for the treatment of intractable epilepsy and depression; yet, its therapeutic efficacy in depression is argued to require further substantiation in controlled settings (Martin & Martin-Sanchez, 2012).

Finally, DBS is a technique that has been used for more than 25 years to modulate dysfunctional neuro-circuitry. It involves the implantation of electrodes in a defined brain target deemed to be central to the clinical problem. Similarly to VNS, the electrodes are connected to a generator implanted in the body, which sends electrical pulses to the region. Marked improvements in the major motor symptoms of Parkinson's disease have been found after DBS typically of either the globus pallidus (GP), sub-thalamic nucleus (STN) or other thalamic targets (DeLong & Wichmann, 2012). Use of DBS now extends into psychiatric disorders for which there are neural-based aetiological models. For example, promising therapeutic effects have been reported following DBS of the subgenual cingulate gyrus or the ventral internal capsule/ventral striatum in major depression (Taghva, Malone, & Rezai, 2012), the nucleus accumbens (NuAcc) in obsessive compulsive disorder (OCD; de Koning et al., 2013; Greenberg et al., 2006) and the hypothalamus in Alzheimer's disease (Laxton et al., 2010).

Neuromodulation based approaches to eating disorders

We have systematically reviewed the effects of such neuromodulatory techniques on ED symptoms and related behaviours, for example food intake and body weight. The need for this review arises from (i) the limited efficacy of existing treatments for ED, in particular enduring AN, (ii) the growing number of neural-based models of ED, (iii) the variety of neuromodulation techniques being used in research and in clinical settings, (iv) recent studies that have applied neuromodulatory procedures in ED patients, and (v) a perceived need to help direct the field of brain-directed interventions in ED.

Methods

A systematic review was conducted, following the recommendations outlined in the PRISMA guidance. The literature search was conducted independently by two investigators and then compared. Any disagreements were resolved by further examination of the full text and via consensus. Relevant studies were identified using online databases Pubmed, PsychInfo and Web of Knowledge. Key search terms are included below in the search strategy used in Pubmed:

((brain stimulation[Title/Abstract] OR "TMS"[Title/Abstract] OR transcranial magnetic stimulation[Mesh Terms] OR "tDCS"[Title/

Abstract] OR "transcranial direct current stimulation"[Title/Abstract] OR transcranial stimulation[Title/Abstract] OR vagus stimulation[Title/Abstract]) AND (food[MeSH Terms] OR food [Title/Abstract] OR eating[MeSH Terms] OR body[MeSH Terms] OR anorexia[MeSH Terms] OR anorexi*[Title/Abstract] OR bulimia[MeSH Terms] OR bulimi*[Title/Abstract] OR obesity [MeSH Terms] OR obes*[Title/Abstract] OR binge eat*[Title/Abstract]))

Searches using Web of Knowledge and PsychInfo were conducted by organising key search terms into two groups. The first group related to neuromodulation techniques, for example ("brain" AND "stimulation"), "TMS", "tDCS", ("transcranial" AND "stimulation"), "VNS" and ("vagus" AND "stimulation"), whilst the second group consisted of ED salient words including "food", "eating", "body", "anorexia", "bulimia", "obesity" and "binge eat". The first group of neuromodulation terms was crossed with each ED salient word.

Initially, all of the identified articles were screened and included on the basis of relevance to the topic via inspection of their title and abstract. Publications were then cross-referenced, published review articles were examined for additional relevant studies and experts in the field were contacted in order to source any additional relevant literature. The full text versions of the remaining articles were then assessed in more detail. An overview of the literature search is shown in Figure 1.

Inclusion/exclusion criteria

We included articles in English (and German) that explored the effects of a form of neuromodulation on eating-related outcomes, for example ED symptoms, food cravings, eating behaviours, food intake, weight and BMI. We included studies on healthy participants, people with ED, and people with other psychiatric or neurological disorders, and studies in animals. In addition to randomised control trials (RCTs), clinical studies, case series and case reports were included.

Several studies were excluded on the basis that their focus was not on changes to eating behaviours or body weight as a result of neuromodulation (e.g. motor excitability in Parkinson's disease). In other cases, studies were excluded that looked primarily at the use of neuromodulation techniques as a conditioned response rather than a neuromodulatory tool. A number of other studies were excluded as they focused on the effects of neuromodulation on bodily form/perception. Whilst this is relevant to ED, it was deemed that this fell out of the scope of the review. Finally, papers reporting on non-eating-related outcomes and safety issues in ED patients (e.g. cortisol concentrations and cardiac safety), and those using an uncommon methods of neuromodulation (e.g. pallidotomy) are not included.

Results

We identified 60 studies that met the inclusion criteria for this review. Five of these were conducted in healthy participants (HP), 6 were in bulimic or obese individuals, 6 were in AN patients, 18 were in individuals with other psychiatric or neurological disorders and 25 were animal studies. The studies that

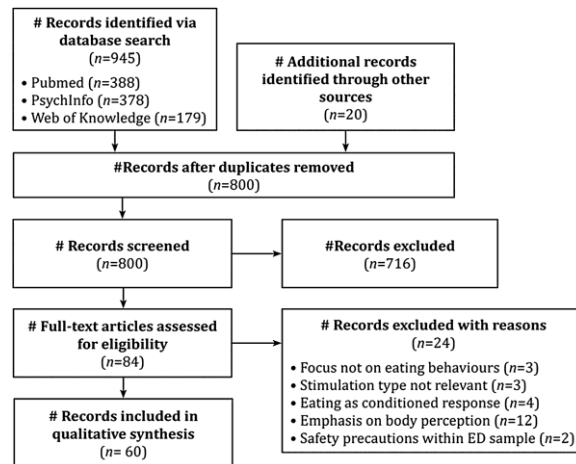


Figure 1. PRISMA flow chart of reviewed studies

were included report effects on ED symptoms, eating behaviours, food intake and changes to body weight associated with the application of neuromodulation techniques to a number of different brain regions/structures illustrated in Figure 2.

Studies in healthy participants and people with frequent food cravings

Five studies in HP were identified, with four of these using individuals who reported frequent food cravings (Table 2). The study involving a non-food craving group reported that compared with control conditions, active low-frequency (1 Hz) rTMS to the right DLPFC decreased the value assigned to food (Camus et al., 2009). Given this, it is arguable that rTMS to the right DLPFC can reduce food cravings. However, following reports of a reduction in the urge to smoke (Johann et al., 2003) and cigarette consumption (Eichhammer et al., 2003) following high-frequency (10 Hz) rTMS to the left DLPFC, two studies used a similar protocol to investigate effects on food cravings (Barth et al., 2011; Uher et al., 2005). In an RCT of 28 individuals, food cravings during exposure to food remained stable after real rTMS and increased after sham (placebo) stimulation (Uher et al., 2005). In contrast, a crossover study with an 'improved' sham condition in ten food cravers reported that real rTMS was no better than sham in reducing cravings (Barth et al., 2011).

Building on the aforementioned studies, Fregni et al. (2008) compared both tDCS protocols, anode right/cathode left and anode left/cathode right, to sham stimulation and found that food cravings reduced, remained stable or increased in these conditions, respectively. Goldman et al. (2011) compared a single tDCS condition, anode right/cathode left, to sham and found food cravings reduced in both conditions; however, the percentage change was greater following the active tDCS.

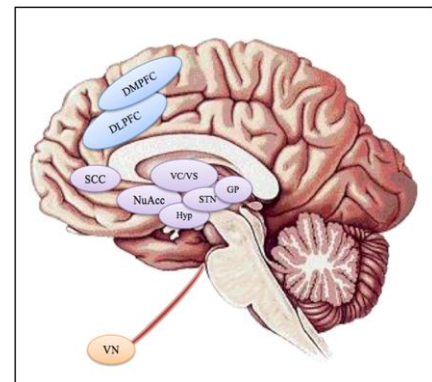


Figure 2. Brain areas targeted in reviewed studies. TMS and tDCS (blue): DMPFC, dorsomedial prefrontal cortex; DLPFC, dorsolateral prefrontal cortex. DBS (purple): SCC, subgenual cingulate cortex; NuAcc, nucleus accumbens; VC/Vs, ventral capsule/striatum; Hyp, hypothalamus; STN, sub-thalamic nucleus; GP, globus pallidus. VNS (orange): VN, vagus nerve

Studies in people with bulimia nervosa, binge eating disorder and obesity

Six studies were identified (Table 3), five of which investigated the effects of rTMS in patients with BN. Two single case studies of patients with BN and comorbid depression applied rTMS either to the left DLPFC (Hausmann et al., 2004) or both sides of the DMPFC (Downar, Sankar, Giacobbè, Woodside, & Colton, 2012).

Table 2 Studies in healthy participants and people with frequent food cravings

	<i>N</i>	Sample	Type	Design	Area	Protocol	Findings	Comments
Camus <i>et al.</i> (2009)	56	HP Right handed	rTMS	Between subjects parallel, blinded (i) real to right DLPFC, 2 controls: (ii) real to vertex and (iii) sham to right DLPFC	Right DLPFC and vertex	1 Hz, 15 minutes 50% output 900 pulses 1 session neuronavigated	Compared with control conditions, real rTMS to right DLPFC decreased the value assigned to food stimuli	
Uher <i>et al.</i> (2005)	28	HP Right handed Frequent food cravings	rTMS	RCT parallel, double blind (i) real versus (ii) sham	Left DLPFC	10 Hz, 20 minutes, 110% MT 1000 pulses 1 session 5 cm anterior method	Food cravings during food exposure remained stable after real rTMS and increased after sham rTMS.	
Barth <i>et al.</i> (2011)	10	HP Frequent food cravings	rTMS	RCT crossover, blinded (i) real versus (ii) sham	Left DLPFC	10 Hz, 15 minutes, 100% MT 3000 pulses 1 session (2 conditions) 5 cm anterior method	Real rTMS reduced cravings no better than sham.	Improved sham condition: matched to individuals' perceived pain.
Fregni <i>et al.</i> (2008)	23	HP Frequent food cravings	tDCS	RCT crossover, double blinded 2 active conditions: (i) anode left/cathode right and (ii) anode right/cathode left versus (iii) sham	DLPFC	2 mA, 20 minutes 1 session (3 conditions) 10–20 EEG system (F3 for left DLPFC, F4 for right DLPFC)	Craving of viewed foods decreased with anode right/cathode left, remained stable with anode left/cathode right and increased after sham. Subjects fixated (eye-tracking) on food-related pictures less after anode right/cathode left. Subjects consumed less food after both types of active stimulation.	
Goldman <i>et al.</i> (2011)	19	HP Frequent food cravings	tDCS	RCT crossover, blinded (i) anode right/cathode left versus (ii) sham	DLPFC	2 mA, 20 minutes 1 session (2 conditions) 10–20 EEG system (F3 for left DLPFC, F4 for right DLPFC)	Food cravings reduced in both conditions; however, percentage change was significantly greater in active tDCS. Active tDCS reduced cravings for sweet foods and carbohydrates more than sham. No difference between groups in amount of food ingested.	

Note: HP, healthy participants; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; DLPFC, dorsolateral prefrontal cortex; MT, motor threshold.

Both case studies reported complete recovery from binge/purge symptoms.

Three studies that involved larger samples (two are RCTs) applied rTMS to the left DLPFC. A therapeutic trial in 14 people with BN of 15 sessions of high-frequency, neuronavigated (guided by structural MRI scans) real/sham rTMS reported improvements in binge/purge behaviours in both groups, with no difference between conditions (Walpoth *et al.*, 2008). In a larger sample of

38 bulimic individuals, our group found that compared with sham, a single session of real rTMS (combined with cue exposure to food) significantly reduced right-handed patients' urge to eat and binge eating episodes over the 24 h following stimulation; however, mood deteriorated in a series of left-handed participants (Van den Eynde, Broadbent, *et al.*, 2010; Van den Eynde, Claudino, *et al.*, 2010).

Only one study has examined neuromodulatory effects in obesity, and no study was found in BED. Montenegro *et al.* (2012)

Table 3 Studies in people with bulimia nervosa and obesity

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Hausmann et al. (2004)	1	BN/DP	rTMS	Case report	Left DLPFC	20 Hz, ~12 minutes, 80% MT 10 sessions; 2 per weekday for 2 weeks MRI guided	After treatment complete recovery from binge/purge symptoms and almost 50% decrease in depression scores. Improvement in self-reported binge/purge behaviours, depressive and OCD symptoms in both groups. No difference between real and sham groups.	
Walpoth et al. (2008)	14	BN	rTMS	RCT parallel, double blind (i) real versus (ii) sham	Left DLPFC	20 Hz, ~12 minutes, 120% MT Total of 30 000 pulses 2000 pulses p/session 15 sessions; 1 per weekday for 3 weeks MRI guided	Compared with sham, real rTMS was associated with a decrease in self-reported urge to eat and binge eating (24 hours post-treatment). No difference between groups in hunger, tension, mood and urge to binge eat.	
Van den Eynde, Claudino et al. (2010)	38	BN right handed	rTMS	RCT parallel, double blind (i) real versus (ii) sham	Left DLPFC	10 Hz, 20 minutes, 110% MT 1000 pulses 1 session 5 cm anterior method	Left-handed group: decrease in reported cravings, whilst urge to eat remained stable. Mood deteriorated in the left-handed group yet improved in the right handed group. No difference between right-handed and left-handed groups in urge to eat, urge to binge, tension or hunger.	Full remission for 64 days. Three single binge/purge episodes due to significant psychosocial
Van den Eynde, Broadbent et al. (2012)	7	BN left-handed	rTMS	Case series All received real despite being told they might receive real or sham. Compared with group in earlier study.	Left DLPFC	10 Hz, 20 minutes, 110% MT 1000 pulses 1 session 5 cm anterior method	(a) Full remission of binge/purge episodes and depression for more than 2 months post-treatment completion.	
Downar et al. (2012)	1	BN/DP	rTMS	Case report	DMPFC (both)	10 Hz, 15 minutes, 120% MT 3000 pulses 40 sessions in total neuronavigated		

Table 3 Continued

N	Sample	Type	Design	Area	Protocol	Findings	Comments
Montenegro et al. (2012)	9 OB	tDCS	RCT	DLPFC	(a) 20 sessions; 1 per weekday for 4 weeks (b) Repeat second course requested (20) 2 mA, 20 minutes, 1 session (4 conditions) 10–20 EEG system (f3 for left DLPFC)	(b) After significant life stressor, requested repeat course. Remained in remission from ED and depression. Compared with sham, active anodal left DLPFC tDCS decreased desire to eat. Anodal left tDCS combined with aerobic exercise led to greater suppression of desire to eat than tDCS/exercise alone.	stressor leading to repeat course.

Note: DP, depression; OB, obesity; rTMS, repetitive transcranial magnetic stimulation; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; MT, motor threshold.

conducted a small crossover study of anode left/cathode right tDCS versus sham stimulation, isolated or combined with aerobic exercise in nine obese individuals. Although this used an opposing stimulation protocol to studies that have reported a reduction in food cravings (anode right/cathode left tDCS), participants' desire to eat decreased after active tDCS in comparison with sham, with a greater decrease being seen when tDCS was combined with aerobic exercise.

Studies in people with anorexia nervosa

Six studies investigating the effects of neuromodulation in patients with AN were identified (Table 4). In a case of AN with comorbid depression, 10 sessions of rTMS to the left DLPFC were initially administered as a treatment for depression (Kamolz, Richter, Schmidtke, & Fallgatter, 2008). As improvements in both depression and AN symptoms (including weight gain) were observed, a further 31 sessions were administered along with maintenance sessions: this resulted in a continuous improvement in both the depression and AN symptoms. A pilot study by our group examined the effect of a single session of real rTMS applied to the left DLPFC in 10 cases with AN and reported a reduction in levels of feeling full, feeling fat and anxiety (Van den Eynde, Guillaume, Broadbent, Campbell, & Schmidt, 2011).

Four studies were identified that used DBS to treat AN. Two cases of AN were treated with DBS for different comorbidities. In the first, there was complete remission of AN in a patient treated with DBS targeting the subgenual cingulate cortex (SCC) for comorbid depression (Israel, Steiger, Kolivakis, McGregor, & Sadikot, 2010). Similar reductions in AN symptoms and the maintenance of a healthy BMI were observed in another patient who underwent DBS (targeting the ventral capsule/striatum) for comorbid OCD (McLaughlin et al., 2013).

Since these promising case reports, two groups have conducted small case series of DBS in AN. In four acutely ill adolescent AN patients, DBS to the NuAcc resulted in an average weight increase of 65% and in all patients no longer meeting diagnostic criteria for the illness (Wu et al., 2012). A recent study applied DBS to the SCC in six treatment-resistant AN patients (Lipsman et al., 2013). Nine months after DBS surgery, three patients (50%) increased and maintained their BMI greater than their historical baseline, whilst four saw improvements in AN-related obsessions, mood, anxiety and affective regulation. Along with these clinical improvements, reversals in the abnormalities seen in the anterior cingulate cortex, insula and parietal lobe were accompanied by changes in cerebral glucose metabolism.

Studies assessing eating behaviours and weight in people with other psychiatric or neurological disorders

Eighteen studies applied neuromodulation to patients with other psychiatric or neurological disorders and found concurrent changes to food cravings, eating behaviours, weight and/or BMI. Findings in patients with OCD, depression and epilepsy are presented in Table 5, followed by studies in Parkinson's disease.

In a single case report of DBS for OCD (targeting the NuAcc), the patient's weight increased by 8 kg in the first few months of treatment (Mantione, van de Brink, Schuurman, & Denys 2010). Following the initial weight increase, this patient weighed 115 kg

Table 4 Studies in people with anorexia nervosa

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Kamolz et al. (2008)	1	AN/DP	rTMS	Case report	Left DLPFC	10 Hz, 20 minutes, 110% MT 2000 pulses 41 sessions in total	(a) Improvement in depression and ED symptoms, for example uncomplicated food intake, less negative cognitions and weight gain. (b) Reduction in depressive symptoms. (c) Significant reduction in depressive symptoms, and participation in eating programme proved to be effective after these 10 sessions. (d) Maintenance sessions administered. Continuous improvement of depression and ED symptoms.	Maintenance sessions required to reduce the chance of a second relapse.
Van den Eynde et al. (2011)	10	AN Right handed	rTMS	Case series All received real despite being told they might receive real/sham.	Left DLPFC	10 Hz, 20 minutes, 110% MT 1000 pulses 1 session 5 cm anterior method for 8 weeks	Real rTMS resulted in reduced levels of feeling full, fat, and anxiety. Trend towards a decrease in urge to exercise. No difference in urge to restrict, urge to eat, mood, tension and hunger. Remission of ED, no relapse and maintained average BMI of 19.1. Remission from ED remained despite depressive breakthroughs. Average of 65% increase in body weight at 38 month follow-up. All patients weighed >85% of expected body weight, menstruation restored and no longer met the AN diagnostic criteria. Depression and OCD symptoms improved. There was reduction in food/eating-related concerns. Food intake, food variety and body weight were increased. BMI maintained between 18.9 and 19.6	
Israel et al. (2010)	1	AN/DP	DBS	Case report	SCC	Right-sided intermittent, 2 minutes on/1 minute off 130 Hz, 5 mA, 91 μ S		Pharmacological treatments continued post-operatively.
Wu et al. (2012)	4	AN	DBS	Case series	NuAcc Bilateral	—		Patients age 16–17 years, duration of illness 13–28 months. All had psychiatric comorbidities.
McLaughlin et al. (2013)	1	AN/OCD	DBS	Case report	VC/V5 Bilateral	120 Hz, 7.5 V, 120 μ S Monopolar		Symptoms worsened when cathode electrode was added.

Table 4 Continued

N	Sample	Type	Design	Area	Protocol	Findings	Comments
Lipsman et al. (2013)	6 AN	DBS	Prospective case series	SCC	130 Hz, 5–7 V, 90 μ s	At 9 months follow-up, 3 patients (50%) increased and maintained BMI greater than their historical baseline. Improvement in food/weight preoccupations, mood, anxiety, affect regulation and quality of life. Changes in cerebral glucose metabolism and reversal of abnormalities in variety brain regions.	Patients age 20–60 years, treatment resistant. Side effects include panic attacks, nausea, air embolus, pain and seizure (1 patient only).

Note: DP, depression; OCD, obsessive compulsive disorder; rTMS, repetitive transcranial magnetic stimulation; DBS, deep brain stimulation; DIPFC, dorsolateral prefrontal cortex; SCC, subgenual cingulate cortex; NuAcc, nucleus accumbens; VCVS, ventral striatum/capsule; MT, motor threshold.

and made a conscious decision to lose weight and successfully lost 44 kg.

Three papers (relating to two studies) report effects of VNS on food cravings and weight changes in depressed patients. Compared with controls, significant changes to cravings of sweet foods (in both directions) between VNS, on/off conditions in depressed participants were reported (Bodenlos, Kose, Borckardt, Nahas, Shaw, O'Neil, & George, 2007; Bodenlos, Kose, Borckardt, Nahas, Shaw, O'Neil, Pagoto, et al., 2007). In contrast, Pardo et al. (2007) examined the effects of VNS in depressed, obese patients and found significant, effortless weight loss proportional to BMI.

Three studies of VNS in patients with epilepsy retrospectively examined changes in weight/BMI following surgery. One study reported a significant weight loss following VNS, for example in 17/27 (63%) patients (Burneo, Faught, Knowlton, Morawetz, & Kuzniecky, 2002), whilst the remaining two studies reported no significant weight change following VNS for epilepsy in both adults (Koren & Holmes, 2006) and children (Kansagra, Ataya, Lewis, Gallentine, & Mikati, 2010; Koren & Holmes, 2006).

The remaining studies report (many retrospectively) changes to eating behaviours and body weight following DBS to either the STN or GP (for the treatment of Parkinson's disease). All 11 studies report either over-eating and/or increases in cravings, weight gain and BMI following DBS (Bannier et al., 2009; Locke et al., 2011; Macia et al., 2004; Montaurier et al., 2007; Novakova et al., 2011, 2007; Sauleau et al., 2009; Strowd et al., 2010; Tuite et al., 2005; Walker et al., 2009; Zahodne et al., 2011).

Studies assessing food intake and weight in animals

Table 6 summarises the 25 animal studies that investigated the effects of neuromodulation on food intake and/or body weight. Three examined the feasibility of DBS as a potential treatment for ED, specifically AN. Lacan et al. (2008) implanted the ventromedial hypothalamus of two monkeys and reported significant increases in food intake with active high-frequency DBS compared with inactive DBS. Despite this, there was no change in body weight during the 4-month study period. The remaining two studies investigated the effects of DBS [sometimes referred to as electrical brain stimulation (EBS)] of the lateral hypothalamus (Welkenhuysen, Van Kuyck, Das, Sciote, & Nuttin, 2008) and NuAcc (van der Plasse, Schrama, van Seters, Vanderschuren, & Westenberg, 2012) in rats. The first found no significant changes to food intake, but the latter reported that DBS of the medial shell of the NuAcc (but not to the core or lateral shell) increased food intake by up to 250% (van der Plasse et al., 2012).

Eight studies examine the effects of VNS and DBS in binge eating/obesity animal models. Three RCTs demonstrate decreased food consumption and/or lowered weight gain in pigs (Sobocki, Fourtanier, Estany, & Otal, 2006; Val-Laillet, Biraben, Randuineau, & Malbert, 2010) and rats (Bugajski et al., 2007) following active VNS.

Four studies applied DBS to the hypothalamus in rats (Sani, Jobe, Smith, Kordower, & Bakay, 2007; Torres, Chabardes, & Benabid, 2012a), monkeys (Torres, Chabardes, Piallat, Devergnas, & Benabid, 2012b) and pigs (Melega, Lacan, Gorgulho, Behnke, & De Salles, 2012). High-frequency DBS to the lateral hypothalamus in rats resulted in sustained weight loss (Sani et al., 2007), whilst

Table 5 Studies assessing eating behaviours and weight in people with other psychiatric and neurological disorders

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Mantione et al. (2010)	1	OCD	DBS	Case report	NuAcc	185 Hz, 3.5 V, 90 microseconds Monopolar	First few months post-surgery weight gain of 8 kg. Then, after conscious decision to lose weight (weighing 115 kg), 10 months after dieting was at target weight of 71 kg (BMI = 25). Maintained weight at 2 years follow-up. Groups did not differ in mean food cravings and their ability to resist food. Between viewing food images, cravings for sweet foods differed between groups: depressed VNS had higher change scores for craving of sweets than depression non-VNS and HC.	Simultaneous effortless smoking cessation.
Bodenlos, Kose, Borkardt, Nahas, Shaw, O'Neill, & George, 2007; Bodenlos, Kose, Borkardt, Nahas, Shaw, O'Neill, Pagoto, et al., 2007	33	DP	VNS	(a) Between groups comparison: (i) depression VNS, (ii) depression non-VNS and (iii) HC (b) Within VNS group: crossover, blinded VNS (i) on versus (ii) off	Left VN	20 Hz, 1.25 mA 0.5–84 months 1 session	Significant, effortless weight loss proportional to initial BMI. Stimulation parameters had no effect on weight changes. Significant weight loss (>5%) in 17 patients. Remaining patients had no significant change in weight. No significant change in weight within 2 years following VNS implantation.	In VNS group, cravings for sweets changed in both directions. Decrease in six participants, increase in five.
Pardo et al. (2007)	14	DP/OB	VNS		Left VN	30 Hz, 0.25–1.5 mA 250 or 500 microseconds 30 seconds on/5 minutes off 24 months		
Burneo et al. (2002)	27	EP	VNS	Retrospective	Left VN			
Koren et al. (2006)	21	EP	VNS	Retrospective	Left VN	30 Hz, 1.25–3 mA, 500 microseconds 30 seconds on and 5 seconds off 24 months		
Kansagra et al. (2010)	23	EP(c)	VNS	Retrospective	Left VN	–	No significant changes in BMI at 1 year and final time point (mean 4.2 years) following VNS implantation.	
Macia et al. (2004)	33	PD	DBS	Retrospective PD DBS (n = 19) versus PD non-DBS (n = 14)	STN	130 Hz, 1.5–3 V, 90 microseconds Monopolar	18/19 DBS patients had significant weight gain and increase in BMI. Significant reduction in resting EE, no change in daily EE	
Tuite et al. (2005)	27	PD	DBS	Retrospective	STN	–	Significant weight gain up to 12 months after surgery.	
Novakova et al. (2007)	25	PD	DBS	Retrospective	STN Bilateral	–	Average weight gain of 9.4 kg during first follow-up at 1–45 months post-implantation. One year later, decrease in 12 patients, increase in 6 and 3 remained stable.	

Table 5 Continued

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Montaurier et al. (2007)	23	PD	DBS	Prospective	STN	148.0 Hz, 2.7–2.8 V, 69 microseconds	Increase in body weight and fat mass after surgery. Daily EE decreased significantly.	No correlation between reduced EE and weight gain
Walker et al. (2009)	24 HS 39 PD	HS PD	DBS	Retrospective	Bilateral STN Unilateral	—	Compared with preoperative baseline, weight increased by mean of 4.3 kg 1 year following surgery.	
Bannier et al. (2009)	22	PD	DBS		STN		68% patients overweight/obese 3 months post-surgery; increased to 82% at 16 months post-surgery. Significantly higher increase in BMI in STN DBS patients.	
Sauleau et al. (2009)	46	PD	DBS	DBS to STN (<i>n</i> = 32) versus DBS to GPi (<i>n</i> = 14)	STN/GP	130 Hz, 60 microseconds		
Strowd et al. (2010)	182	PD	DBS	Retrospective	STN/VM/ GP	—	Significant weight gain up to 24 months post-surgery, not predicted by stimulation target.	
Novakova et al. (2011)	27	PD	DBS		STN	—	Significant weight gain during 12 month post-implantation.	
Locke et al. (2011)	52	PD	DBS	Retrospective	STN/GP Unilateral	—	Significant weight gain following surgery; no significant difference in weight gain between GP and STN targets.	No correlation between reduced motor scores and weight gain.
Zahodne et al. (2011)	100	PD	DBS	Prospective	STN/GP	—	DBS implantation predicted over eating and an increase in cravings.	

Note: OCD, obsessive compulsive disorder; DP, depression; OB, obesity; EP, epilepsy; EP(c), children with epilepsy; PD, Parkinson's disease; DBS, deep brain stimulation; VNS, vagus nerve stimulation; NuAcc, nucleus accumbens; VN, vagus nerve; STN, sub-thalamic nucleus; GP, globus pallidus; EE, energy expenditure.

Table 6 Studies assessing food intake and weight in animals

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Animal models of anorexia nervosa								
Lacan et al. (2008)	2	Monkeys	DBS	2 cycles of stimulation (a) 8 days of active, 2 days of inactive and (b) 3 days active, 3 days inactive.	vmH Bilateral	(a) 185 Hz, 2.5 V, 90 microseconds (b) 185 Hz, 3.5 V, 90 microseconds	Significant increase in food intake during active stimulation. There was no change in body weight.	
Wellenhuysen et al. (2008)	26	Rats	EBS (DBS)	(a) Acute: 4 subsequent sessions conducted in random order of amp. (b) Chronic: on/off	Lateral hypoth.	(a) 100 Hz, 0.06 millisecond, 3.5 hours, 0%, 25%, 50% and 75% amp. (b) 100 Hz, 0.06 millisecond pulses, 50% maximum amplitude	(a) Decrease in the number of wheel rotations (lower activity levels) but no impact on food intake. (b) No effect on wheel rotations or amount of food consumed.	
van der Plasse et al. (2012)	8	Rats	DBS	Comparison of DBS to 3 areas of NAcc (i) core, (ii) lateral shell (lShell) and (iii) medial shell (mShell)	NAcc	130 Hz 60 µs pulses, 200 µs off 300 µm electrodes	DBS to core had no effect on response to sucrose or food intake, to lShell reduced motivation to respond for sucrose, no effect on food intake. DBS to mShell profoundly increased food intake (250% of baseline).	Implications for medial shell of NAcc as target for DBS in AN.
Animal models of binge eating and obesity								
Sobocki et al. (2006)	8	Pigs	VNS	RCT crossover design (i) 4 weeks on versus (ii) 4 weeks off	Anterior VN	34 Hz, 4 V, 0.5 millisecond, every 3–4 hours for 24 hours	In both groups, cumulative body weight gain was lower during stimulation period compared with the control period.	Metabolic rate not affected.
Bugajski et al. (2007)	18	Rats	VNS	RCT 3 groups: (i) active VNS; (ii) inactive VNS and (iii) no VNS	Left VN Unipolar	0.05 Hz, 200 mV, 10 millisecond pulses 100 days	Significant decrease in meal size, fat weight and weight gain in VNS rats compared with controls.	
Val-Laillet et al. (2010)	8	Mini Pigs	VNS	RCT (i) real versus (ii) sham	VN	30 Hz, 2 mA, 500 µs 30 seconds on/5 minutes off 14 weeks	VNS implantation resulted in animals' weight remaining stable, decreased food consumption and decreased sweet-food cravings compared with animals with sham implants.	
Sani et al. (2007)	16	Rats	DBS	RCT	Lateral hypoth.	180–200 Hz, 2.0 V, 100 millisecond pulse width, ~31 days	Significant decrease in weight gain in the stimulated compared with the non-stimulated group.	
Torres et al. (2012a)	27	Rats	DBS	(i) active continuous stimulation versus (ii) implanted inactive Unilateral continuous, bipolar stimulation	vmH	30–130 Hz, 60 milliseconds, 222 ± 103 µA	(a) Acute HF increased food intake compared with sham.	

Table 6 Continued

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
				(a) Acute: HF (130 Hz) versus LF (30 Hz) (b) Chronic: long-term effects of HF		(a) 30 minutes (b) 16 days, 4 hours/day, 5 days/week, 3 weeks	Acute LF reduced food intake compared with sham. (b) Chronic stimulation (130 Hz) slowed down body weight intake compared with sham.	
Torres <i>et al.</i> (2012b)	5	MK	DBS	(a) Acute: various DBS parameters post 24 hour fasting period versus inactive (b) chronic: 8 week trial of 3 protocols	Hypoth.	(a) 30–130 Hz, 8 hours (b) 30 Hz, 80 Hz, 130 Hz continuous stimulation day/night for 8 weeks.	(a) Decreased food intake for all MK at 80 Hz (b) Significant decrease in body weight and BMI at 80 Hz. Skinfolds reduced at 80 Hz yet increased at 130 Hz. Sham MK increased their weight. All animals ate the same amount of food, yet those that received active DBS had less cumulative weight gain than non-stimulated animals. DBS to NAcc shell reduced binge eating and increased c-Fos levels in this area (measure of neuronal activity). Dopamine receptor D2 attenuated action of DBS. DBS to dorsal striatum had no influence on binge eating. Chronic DBS to obese mice reduced caloric intake and induced weight loss.	Intraventricular approach
Melega <i>et al.</i> (2012)	8	Mini pigs	DBS	2 groups: (i) active versus (ii) inactive	vmH Bilateral	50 Hz, 8 weeks, 507 microseconds 0.5, 1.0, 1.5 mA	(b) Significant decrease in body weight and BMI at 80 Hz. Skinfolds reduced at 80 Hz yet increased at 130 Hz. Sham MK increased their weight. All animals ate the same amount of food, yet those that received active DBS had less cumulative weight gain than non-stimulated animals. DBS to NAcc shell reduced binge eating and increased c-Fos levels in this area (measure of neuronal activity). Dopamine receptor D2 attenuated action of DBS. DBS to dorsal striatum had no influence on binge eating. Chronic DBS to obese mice reduced caloric intake and induced weight loss.	DBS may be associated with increase in metabolic rate.
Halpern <i>et al.</i> (2013)	73	Mice	DBS	Randomised design (a) binge eating: surgical and non-surgical mice (b) acute DBS to NAcc shell or dorsal striatum (c) chronic DBS in diet-induced obese mice	NuAcc shell	(a) 160 Hz, 150 μ A 60 μ S pulses, 1 hour (b) 160 Hz, 150 μ A, 60 μ S pulses for 4 days	DBS to NAcc shell reduced binge eating and increased c-Fos levels in this area (measure of neuronal activity). Dopamine receptor D2 attenuated action of DBS. DBS to dorsal striatum had no influence on binge eating. Chronic DBS to obese mice reduced caloric intake and induced weight loss.	Implicates mesolimbic dopamine pathways in hedonic aspects of obesity.
Other studies in animals								
Laskiewicz <i>et al.</i> (2003)	60	Rats	VNS	5 conditions: (i) left vagal (0.5 Hz), (ii) both vagal nerves (0.5 Hz), (iii) left vagal (0.1 Hz), (iv) both vagal nerves in obese rats (0.1 Hz) and (v) left vagal combined with right side abdominal vagotomy	Left and right VN	0.05 and 0.1 Hz, 0.55 V, 0.1 seconds for 27 days	Body weight and total food intake decreased in all conditions. Effects of both vagal nerves stimulation on final body weight and food intake significantly more effective than only one single nerve.	
Zionber <i>et al.</i> (2009)	78	Rats	VNS	3 conditions (i) active in the magnetic field exposure (MFE), versus 2 control groups with inactive solenoid without electrodes,	Left VN	0.1, 0.2, 0.5 and 1.0 Hz 50, 100, 150 and 200 mV Stimulation changed every 3 days for 15 days	Rats with solenoid electrodes significantly decreased their food intake, weight gain and serum leptin concentrations when compared with controls.	

		(ii) in the MFE and (iii) outside the MFE				
Gil et al. (2011)	24	Rats	VNS	Randomised into 3 groups: (i) active, (ii) inactive and (iii) non-operated controls	Left VN	Active VNS stimulation reduced daily and total food intake, body weight and body fat compared with both inactive and control group. No difference in food intake or body fat between inactive and control condition. Compared with sham, chronic VNS reduced food intake, body weight gain and amount of adipose tissue. Daily stimulation produced increase in food intake.
Banni et al. (2012)	10	Rats	VNS	2 naïve, 4 sham, 4 VNS rats compared across (a) acute (3 hours) and (b) chronic (4 weeks)	Left VN	30 Hz, 1.50 mA 30 seconds on/5 minutes off
Delgado et al. (1953)	6	Cats	DBS	(a) Control period 1–2 weeks before implantation versus (b) bipolar stimulation	Lateral hypoth.	60 Hz, 0.2 microsecond, 1–5 V
Stephan et al. (1971)	14	Rats	EBS (DBS)	On versus off stimulation	Lateral hypoth.	0.5 s, every 5 seconds, 1 hour 5–10 days
Mogenson et al. (1971)	75	Rats	EBS (DBS)	–	Lateral hypoth.	10–60 μ A, 0.5 minute on/1 minute off 20 trials 60 Hz, 6–30 μ A, 5 seconds on/15 seconds off, 30 minutes
Schallert et al. (1977)	38	Rats	EBS (DBS)	Food and water deprivation versus brain stimulation	Lateral hypoth.	100 Hz, 30–90 μ A, 0.2 millisecond, 1 minute on/30 seconds off
Halberin et al. (1983)	8	Rats	EBS (DBS)	4 conditions: (i) saline, inactive EBS, (ii) adrenergic, inactive EBS, (iii) saline, active EBS and (iv) adrenergic, active EBS	Left lateral hypoth.	60 Hz, 14–104 μ A 30 seconds on/30 seconds off, 20 trials
Brown et al. (1984)	6	Dogs	DBS	RCT (i) vmH on/off versus (ii) subcortical white matter (control)	vmH white matter (control)	50 Hz, 100 μ A, 3.5 V 1.0 millisecond (a) deprived food for 24 hours, DBS for 1 hour, repeated with inactive, (b) 1 hour of DBS every 12 hours for 3 days
Stenger et al. (1991)	10	Rats	DBS	3 conditions: (i) vmH stimulated, (ii) extra vmH stimulated and (iii) vmH implanted controls	vmH	50 Hz, 300 μ A, 100 microseconds 20 trains of 60 seconds, 400 milliseconds on/600 milliseconds off, 12 sessions

Emphasis on
copulation behaviours.

Table 6 Continued

	N	Sample	Type	Design	Area	Protocol	Findings	Comments
Bielajew et al. (1994)	49	Rats	EBS (DBS)	2 conditions: (i) vmH and (ii) adjacent areas of vmH	vmH	50 Hz, 300 μ A, 20 trains of 60 seconds 400 milliseconds on/600 milliseconds off, 3 hour duration \times 3 sessions	Stimulation bound activity associated with decrease in weight gain and food intake. Weight gain and food intake not affected by electrode placement.	
Ruffin et al. (1999)	8	Rats	EBS (DBS)	RCT crossover design: (i) active versus (ii) sham	vmH	20–25 μ A, 1 millisecond pulse, 9 millisecond interval 30 seconds on/30 seconds off, 15 minutes	vmH suppressed feeding and increased metabolism. No change with sham.	
Lehmkuhle et al. (2010)	35	Rats	DBS	(i) chronic stimulation versus (ii) 4 control groups	vmH	150 or 500 Hz 10 μ A, 250 microsecond pulses 6 weeks	Stimulated animals gained weight at a lower rate than controls. No significant difference in food intake between groups.	Weight gain altered without affecting feeding behaviours.

Note: EBS/DBS, electrical/deep brain stimulation; VNS, vagus nerve stimulation; vmH, ventromedial hypothalamus; NuAcc, nucleus accumbens; VN, vagus nerve; VMH, ventromedial hypothalamus; MT, motor threshold.

DBS to the ventromedial hypothalamus produced mixed findings. Torres, Chabardes, and Benabid (2012a) found that compared with inactive DBS, high-frequency (130 Hz) DBS increased food intake, whilst low-frequency (30 Hz) DBS reduced food intake in 27 rats. In contrast, Torres, Chabardes, Piallat, et al. (2012b) found that 8 hours of high-frequency (80 Hz) DBS decreased food intake in all five monkeys after fasting and reduced body weight/BMI in three (of four) monkeys after 8 weeks of stimulation. Melega et al. (2012) administered low-frequency DBS to the ventromedial hypothalamus in eight mini pigs given double their amount of daily food for a 2-month period. All animals consumed the food given; however, those who received active DBS showed lower cumulative weight gain than the non-stimulated group.

As far as we are aware, only one animal study has investigated the effects of DBS on binge eating behaviours. Halpern et al. (2013) demonstrated that short-term (1 hour) DBS to the NuAcc (but not the dorsal striatum) reduced binge eating in mice, and chronic stimulation to the NuAcc over 4 days led to a reduction in caloric intake and induced weight loss.

Four studies report changes in food intake and/or body weight in rats following VNS. These studies applied VNS for a period of 15–42 days. All four found a reduction in food intake, body weight/fat and/or weight gain following VNS (Banni et al., 2012; Gil, Bugajski, & Thor, 2011; Laskiewicz et al., 2003; Ziomer et al., 2009).

Finally, 10 studies suggest changes in food intake and weight as a result of DBS to two areas of the hypothalamus. In general, stimulation of the lateral hypothalamus induced food intake in both cats and rats (Delgado & Anand, 1953; Halperin, Gatchalian, Adachi, Carter, & Leibowitz, 1983; Mogenson, 1971; Schallert, 1977; Stephan, Valenstein, & Zucker, 1971). However, a number employed complex protocols involving comparisons with copulatory behaviours (Stephan et al., 1971) or DBS/EBS in conjunction with food deprivation (Schallert, 1977) or adrenergic interventions (Halperin et al., 1983), so their findings lack comparability. DBS/EBS to the ventromedial hypothalamus consistently reduced food intake and/or reduced weight gain (Bielajew, Stenger, & Schindler, 1994; Brown, Fessler, Rachlin, & Mullan, 1984; Lehmkuhle, Mayes, & Kipke, 2010; Ruffin & Nicolaidis, 1999; Stenger, Fournier & Bielajew, 1991).

Discussion

This review provides evidence that neuromodulation has potential for altering disordered eating behaviours, food intake and body weight. Non-invasive neuromodulation techniques (rTMS and tDCS) have been shown to prevent and reduce cravings in individuals who report frequent food cravings, and rTMS applied to the prefrontal cortex also has shown promise for reducing BN symptoms. In AN, the data also demonstrate potential for symptom improvement including weight gain, following both rTMS and DBS. Furthermore, reports of significant weight gain following DBS for Parkinson's disease provide grounds for investigating the use of DBS in AN, whilst VNS may have potential as an alternative bariatric intervention.

Methodological considerations

Findings reported in this review must be interpreted in the context of the varying methodologies considered. Four different techniques, rTMS, tDCS, VNS and DBS, have been reviewed, and within each exists the potential for a wide range of protocols.

Each technique has the ability to suppress/enhance neural activity via a number of different parameters—frequency, duration, intensity, number of pulses, number of sessions and stimulation sites. Such differences may help explain why some studies report no changes in ED symptoms or weight following neuromodulation (Barth *et al.*, 2011; Kansagra *et al.*, 2010; Koren & Holmes, 2006; Walpoth *et al.*, 2008). The degree to which studies vary from one another methodologically also limits their comparability and hence the generalisability of these findings. On the other hand, the number of neuromodulatory techniques available and the wide range of protocol options possible within each means that the field is advancing along a broad front.

Further studies on the neural effects of neuromodulation are needed to optimise protocols: these are likely to arise from research involving online neuroimaging/neuromodulation. Data from animal models are also important but must be interpreted with caution, as factors such as the ratio of neuromodulation device (e.g. TMS coil size) to head size, coil orientation, anaesthesia and mechanical restraint are just a few elements that need to be considered when findings are extrapolated to humans (Vahabzadeh-Hagh, Muller, Gersner, Zangen, & Rotenberg, 2012). Finally, although limited by issues of stimulation focality and differences between animal and human brains, animal models are likely to provide important information on the mechanisms of neuromodulation and their potential for use in the treatment of disorders such as ED.

Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation has been investigated in healthy individuals, in those reporting frequent food cravings, and in patients with BN and AN. Most of this work has involved high-frequency (excitatory) rTMS to the left PFC. The studies demonstrate its promise in stabilising food cravings during food exposure and reducing both BN and AN symptoms. Arguably, this may result from restoring altered 'top-down' cognitive control in relation to emotional and other self-regulation processes. Given the demonstrated ability of rTMS to modulate food cravings and binge eating episodes, in addition to its non-invasive, safe and relatively tolerable nature, it is perhaps surprising that no studies have investigated its potential in BED or obesity. Lastly, given the chronic and life-threatening nature of AN and the promising data on rTMS in AN, larger, sham-controlled studies are needed.

Use of brain imaging techniques in ED is likely to increase knowledge of the neural correlates of disordered eating, and this will enable refinement and optimisation of rTMS protocols for treating specific ED. In particular, the role of right fronto-temporal circuits in ED as outlined in a review of brain lesions in ED (Uher & Treasure, 2005) and reports of ED resolution following right temporal lobe injuries (Levine, Lipson, & Devinsky, 2003) suggest that right-sided rTMS may be equally, if not more, effective than the predominately left-sided rTMS protocols.

Transcranial direct current stimulation

Increased knowledge on the role of hemispheric lateralisation in ED, together with improvements in the design of neuromodulation protocols, is likely to emerge from studies involving tDCS. To date, most tDCS research has been in relation to food cravings and has shown that excitation of the right/inhibition of the left PFC reduces cravings during

cue exposure. Stabilisation of cravings during exposure was observed with the opposite tDCS protocol, which is somewhat consistent with the rTMS literature. The idea that increasing activity in the right PFC may decrease cravings/appetite and re-establish control over eating is also consistent with the right brain hypothesis of obesity (Alonso-Alonso & Pascual-Leone, 2007). It is possible that there is some type of inter-hemispheric imbalance in conditions involving cravings and over eating, but more neuroimaging-based evidence is required.

In comparison, the idea of right hemispheric dominance in AN, specifically hyperactivity in the right frontal regions, is somewhat established, and it is possible that anodal left/cathodal right tDCS may aid in altering/resetting inter-hemispheric balance (Hecht, 2010). This is consistent with the TMS literature in AN, which shows symptom reduction following excitation of the left DLPFC. By comparing the two possible tDCS designs to sham tDCS in AN, the possible role of hemispheric lateralisation in the illness may be elucidated. As in the case of rTMS, there is a need for more investigations of tDCS within ED populations.

Vagus nerve stimulation

Evidence from the use of VNS in other psychiatric and neurological disorders and in animal studies supports the argument for more investigations in ED, including obesity. Whilst VNS seems to have induced weight loss in a proportion of participants with depression, obesity or epilepsy, VNS in animals has consistently been associated with reductions in food intake and/or weight loss.

The vagus nerve is the major neural pathway carrying information to the gastrointestinal tract. In the current review, VNS has been associated with changes in food intake and resulting body weight, suggesting that vagal stimulation mediates satiety signals. Given the increasing prevalence, high morbidity and mortality of obesity, VNS has potential as an alternative to more invasive treatments for morbid obesity, which are often associated with severe side effects and unsustainable weight loss.

Deep brain stimulation

Deep brain stimulation has been used in a number of treatment studies of AN, in part as a result of emerging neural-based models of AN. The results are promising—two case reports resulting in remission of the illness, and two case series resulting in increases in body weight and reductions in symptoms in most patients. Furthermore, the reviewed cases have demonstrated DBS to be a safe procedure with minor side effects. Existing studies of DBS in AN have targeted a variety of different brain structures, and thus, more research is needed in order to establish optimal DBS targets. Moreover, larger controlled trials are needed to establish the long-term efficacy of DBS in this difficult to treat population.

Weight gain following DBS for Parkinson's disease has implications for the use of DBS in AN. Although the reduction in motor activity (e.g. tremors) as a result of DBS may contribute to resulting weight gain, two studies found no correlation between weight gain and reduced motor activity following DBS (Locke *et al.*, 2011; Montaurier *et al.*, 2007). A number of explanations have been proposed including the suggestion that the DBS current may spread to the hypothalamic satiety centres. In support of this, a number of animal studies report increases in food intake and/or body weight following DBS to the lateral hypothalamus. In contrast, stimulation

to the ventromedial hypothalamus shows the opposite, particularly when applied at lower frequencies. Interestingly, two studies showed lower rates of weight gain in stimulated animals despite no changes in the amount of food consumed, suggesting that DBS may alter metabolic rate (Lehmkühle et al., 2010; Melega et al., 2012).

Considerations for neuromodulation in eating disorders

Eating disorders are complex, multifaceted mental illnesses, associated with altered thinking and beliefs, heightened fear and anxiety responses, mood disturbances and a myriad of other symptoms. The ED are therefore not simply about eating. Although this review reports solely on the effects of neuromodulation on eating-related behaviours and resulting weight gain/loss, such changes are likely to arise as a result of effects to some of the underlying cognitive, emotional and self-regulatory aspects of ED, such as cognitive rigidity, impaired decision making, poor inhibition and altered self-control. Such traits are proposed to be caused by the same dysfunctional fronto-subcortical circuits (Celone et al., 2011; Marsh et al., 2011; Marsh, Steinglass, et al., 2009; Sato et al., 2013). Neuromodulation is likely to alter such neurocognitive impairments in ED; however, further investigations employing neuropsychological outcomes are required.

Changes in neuropsychological aspects of ED following neuromodulation may also result from alterations associated with neuroplasticity. Studies in animals have demonstrated that repeated sessions of high-frequency rTMS induce long-lasting effects in neuroplasticity (Gersner, Kravetz, Feil, Pell, & Zangen, 2011). Such findings have implications for intractable, neuro-circuit disorders such as AN. Changes in neuroplasticity highlight the potential of including exposure therapies with neuromodulation protocols in ED, to facilitate extinction learning (Koskina, Campbell, & Schmidt, 2013). In rats, high-frequency TMS paired with exposure to a conditioned stimulus facilitated fear extinction up to 24 hours post-stimulation (Baek, Chae, & Jeong, 2012). Whilst a number of studies reviewed here include exposure to highly palatable foods immediately before and after neuromodulation, online approaches applying neuromodulation during exposure tasks may improve outcomes.

Similarly, individual differences in cortical plasticity have been shown to modulate the behavioural effect of neuromodulation (Plewnia et al., 2013). Research into individual neural patterns will enable more precise, personalised protocols for rTMS, tDCS, VNS and DBS. Altering neuromodulation parameters such as stimulation site and frequency (excitatory/inhibitory) as a result of a better understanding of hemisphere lateralisation and hyperactivity or hypoactivity of certain brain regions is one likely possibility. In addition, brain imaging could be used to identify biomarkers of treatment response and thus individualised neuromodulation foci.

Such neural targets may include the insula and other subcortical structures involved in emotional responses and reward processing, and implicated in brain imaging ED research. However, the neural effects of common non-invasive neuromodulation techniques such as rTMS and tDCS are thought to be limited to the outer cerebral cortex. Continuing innovation within the neuromodulation domain has led to the development of tools with both improved focality and a greater depth of modulatory effects. Deep TMS operates on the same principle of electromagnetic induction as standard TMS. However, the standard TMS figure-of-eight coil alters cortical excitability up to a depth of 1.5–2.5 cm. In comparison, the most widely used and safety-tested deep TMS coil—the H-coil—exerts neuromodulatory effects up to 6 cm from the scalp (Bersani et al., 2013; Zangen, Roth, Voller, & Hallett, 2005). Early evidence suggests that patients with treatment-resistant depression who are also ECT non-responders may benefit from deep TMS (Rosenberg, Zangen, Stryker, Kotler, & Dannon, 2010). Deep TMS may therefore have a place in future ED neuromodulation applications. Modulation of both the cerebral cortex and limbic neural circuits that deep TMS may induce could enable changes to both the dysfunctional ‘top-down’ dorsal circuits as well as the ‘bottom-up’ ventral systems proposed to underlie ED. Similarly, building on advances from TMS research, magnetic seizure therapy (MST) induces a seizure via high-frequency TMS. Despite the same final outcome as ECT, that is, a ‘therapeutic’ seizure—increased stimulation focality, lessened side effects in conjunction with similar antidepressant response rates to ECT have been found in the early stage of MST investigations, indicating that this a preferable alternative (Hoy et al., 2013).

Conclusions

Increasing knowledge of the neural underpinnings of ED, and the evidence emerging from neuromodulation studies, indicates that treatments for ED will not remain ‘brainless’. Although neuromodulation treatments are unlikely to be stand-alone treatments for ED or obesity, this review demonstrates the potential of rTMS, tDCS, VNS or DBS to improve outcomes when coupled with current therapeutic interventions. In particular, reducing problematic eating behaviours and promoting weight gain in enduring and chronic cases of AN seem feasible via the use of neuromodulation techniques.

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Appendix A.2 Therapeutic case series (Chapter 5)

CASE REPORT

Improvements in Symptoms Following Neuronavigated Repetitive Transcranial Magnetic Stimulation (rTMS) in Severe and Enduring Anorexia Nervosa: Findings from two Case Studies

Jessica McClelland^{1*}, Natali Bozhilova¹, Steffen Nestler¹, Iain C. Campbell¹, Shirabdi Jacob², Eric Johnson-Sabine² & Ulrike Schmidt¹

¹King's College London, Institute of Psychiatry, UK

²Phoenix Wing, St Ann's Hospital, UK

Abstract

Background: Advances in the treatment of anorexia nervosa (AN) are most likely to arise from targeted, brain-directed treatments, such as repetitive transcranial magnetic stimulation (rTMS). We describe findings from two individuals with treatment-resistant AN who received 19–20 sessions of neuronavigated, high frequency rTMS, applied to the left dorsolateral prefrontal cortex.

Method: Within-session measures assessed changes pre-rTMS, post-rTMS in subjective eating disorder (ED) experiences. Weight, ED symptoms and mood were assessed pre-treatment, post-treatment and at 1 month follow-up.

Results: In both cases, there was improvement in ED symptomatology and mood after 19–20 sessions of neuronavigated rTMS, and these changes persisted or continued to improve at follow-up. Within sessions, Patient A demonstrated a consistent reduction in subjective ED experiences, and Patient B a reduction in some ED related experiences.

Conclusions: These findings suggest that rTMS has potential as an adjunct to the treatment of AN and deserves further study. Copyright © 2013 John Wiley & Sons, Ltd and Eating Disorders Association.

Keywords

anorexia nervosa (AN); repetitive transcranial magnetic stimulation (rTMS); dorsolateral prefrontal cortex (DLPFC)

*Correspondence

Jessica McClelland, P059, Section of Eating Disorders, Institute of Psychiatry, King's College London, De Crespigny Park, London SE58AF, UK. Phone: +44(0)2078480183. Email: jessica.mcclelland@kcl.ac.uk

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Introduction

Anorexia nervosa (AN) is a life-threatening mental illness, which severely impairs quality of life. It is characterized by an intense fear of food, eating and gaining weight, severe food restriction and in some cases binge/purge behaviours, resulting in extremely low body weight. AN is associated with a myriad of physical and psychological comorbidities, high levels of mortality and disability (Arcelus, Mitchell, Wales, & Nielsen, 2011). Given the typically adolescent onset, the illness blights a key developmental period. The median duration of AN is from 5 to 7 years (Zipfel, Lowe, Reas, Deter & Herzog, 2000) however about a quarter of sufferers have a particularly severe and enduring form of the illness that lasts for longer than 10–15 years (Steinhausen, 2002). There is uncertainty about the management of adult patients with AN *per se* (NICE, 2004) (Schmidt et al., 2012; Watson & Bulik, 2012), but especially regarding those with a severe and enduring form of the illness who typically will have undergone multiple psychological and pharmacological treatments and unsuccessful attempts to restore a healthy weight in inpatient treatment (Hay, Touyz, & Sud, 2012). This situation underscores the need to develop new treatments.

Significant advances have been made over the last decade in our understanding of the neural correlates of AN, with research highlighting both structural (Frank, Shott, Hagman, & Yang,

2013; Mainz, Schulte-Ruther, Fink, Herpertz-Dahlmann, & Konrad, 2012; Van den Eynde et al., 2012) and functional (Brooks et al., 2011; Frank & Kaye, 2012; Kim, Ku, Lee, Lee, & Jung, 2012; Pietrini et al., 2011; Uher et al., 2004; Zhu et al., 2012) alterations in the brain of AN sufferers. Generally speaking, such neuroimaging studies demonstrate gray and white matter alterations, and disturbances in limbic, frontal and parietal areas, in addition to alterations in the functioning of neurotransmitters including serotonin and dopamine at different stages of AN.

Drawing from such findings, many argue AN as a neural circuit-based disorder (Kaye, Fudge, & Paulus, 2009; Kaye, Wagner, Fudge, & Paulus, 2011; Marsh, Maia, & Peterson, 2009; van Kuyck et al., 2009). These neural models propose that AN may partly result from alterations in ventral circuits controlling interoceptive and reward processing, combined with dysregulation in dorsal, cognitive circuits. In response to altered reward and emotionality surrounding food/eating disorder (ED) cues, self regulation difficulties such as the excessive self-control characteristic of AN, is likely to derive from disturbances in frontostriatal circuits involving areas such as the dorsolateral prefrontal cortex (DLPFC).

Because of its central role in decision making (Plassmann, O'Doherty, & Rangel, 2007) and emotion regulation (Ochsner & Gross, 2005), the DLPFC is a common target for neuromodulation interventions in other neural circuit-based disorders. For example,

repetitive transcranial magnetic stimulation (rTMS) to the left DLPFC has demonstrated clinical efficacy and is approved by the US Food and Drug Administration as a second-line treatment for depression (O'Reardon et al., 2007). Neuromodulation techniques such as rTMS have the ability to alter neural activity in a variety of ways and are being used within both research and clinical settings for a wide range of neurological and psychiatric disorders (Slotema, Blom, Hoek, & Sommer, 2010).

Although research involving rTMS in ED is in its infancy, existing animal and human literature suggests its potential for altering ED related symptoms (McClelland, Bozhilova, Campbell, & Schmidt, 2013). To date, three studies investigating the effects of rTMS on ED related symptoms in healthy participants (e.g. food cravings) and five studies in bulimia nervosa (BN) exist. Findings from such work range from a lack of clinical improvement following rTMS (Barth et al., 2011; Walpoth et al., 2008), the prevention and reduction of food cravings (Uher et al., 2005; Van den Eynde et al., 2010), to complete remission of BN in two case studies (Downar, Sankar, Giacobbe, Woodside, & Colton, 2012; Hausmann et al., 2004).

Along with the growing neuroimaging data supporting the neural-circuit model of AN, support for the use of rTMS in AN comes from a successful case report where 20 sessions of rTMS to the left DLPFC treated comorbid depression and improved ED symptoms (including weight gain) in an individual with AN (Kamolz, Richter, Schmidtke, & Fallgatter, 2008). Since then, our group has conducted a pilot study of a single session of rTMS to the left DLPFC (coupled with cue exposure) in 10 AN individuals and demonstrated a reduction in levels of anxiety, feeling full and feeling fat—some of the core self-regulation difficulties characteristic of the illness (Van den Eynde, Guillaume, Broadbent, Campbell, & Schmidt, 2011).

On the basis of the neuroscience data described previously and the ability of rTMS to alter ED related symptoms, we aimed to assess the therapeutic efficacy of rTMS in two individuals with AN. With improved investigatory techniques than used previously, that is, using neuronavigation/magnetic resonance imaging (MRI) guided rTMS, we hypothesise that such intervention would:

1. improve ED related to subjective experiences and self-regulation abilities following food cue exposure and
2. encourage weight gain, improve ED symptomatology and mood.

Methods

Patients

Two patients with a Diagnostic and Statistical Manual for Mental Disorders diagnosis of AN (Patient A; restrictive, purging sub-type

and Patient B; binge-purge) volunteered to take part in the study. Both patients were recruited following their participation in an ongoing randomized controlled trial (RCT) of a single session of real or sham rTMS, before committing to the current study. Contraindications to rTMS were checked with the TMS Adult Safety Screening Questionnaire (Keel, Smith, & Wassermann, 2001) and patients met the principal eligibility criterion required, that is, a body mass index between 14–18.5 kg/m². Exclusion criteria were being on a dose of psychotropic medication that had not been stable for at least 14 days prior to enrolment, pregnancy, excessive nicotine use (>20 cigarettes/day) or substance dependence. Local ethical committee approval was obtained for both the experimental RCT and for subsequent therapeutic rTMS (REC ref: 12/LO/1525), and written informed consent was obtained from both patients. Demographic and clinical information for both Patient A and Patient B can be found in Table 1. Patient A was a 23 year old woman who had been treated as an inpatient for approximately 12 years and thus suffered from a particularly severe and enduring form of AN. Patient B was a 52 year old woman who also had very longstanding AN of the binge/purge type.

Procedures and outcomes

Patients attended three rTMS sessions per week (Monday, Wednesday and Friday) for the first 2 weeks/six sessions of treatment. Following this, session frequency was increased to five sessions per week (Monday–Friday) for the remaining sessions. Both patients were due to complete the 20 sessions, whilst Patient A did, Patient B missed one of her 20 planned sessions as a result of her reporting a single episode of being dizzy/dazed following a session. Sessions were resumed as planned, after physical checks were normal, but due to time constraints she received a total of only 19 sessions.

Both participants underwent a structural MRI scan, which was later used with Brainsight® to neuronavigate the TMS coil to the location of the left DLPFC. The imaging protocol included a high-resolution sagittal 3D T1-weighted magnetization prepared rapid gradient echo volume (voxel size 1.1 × 1.1 × 1.2 mm³) which was obtained using a customized pulse sequence (Jack et al., 2008). Full brain and skull coverage was required, and detailed quality control was carried out on all MRI data according to previously described quality control procedure (Simmons et al., 2009, 2011). A Magstim Rapid device and figure-eight coil (Magstim, UK) were used to apply the rTMS. After mapping and recording the abductor pollicis brevis site in the left motor cortex, each participant's motor threshold (MT) was defined as the minimum stimulator output required to evoke 5 out of 10 motor evoked potentials greater than 50 µV. Each individual's MT was re-evaluated on a weekly basis and 20 trains of rTMS were delivered to the left DLPFC using Brainsight® software

Table 1 Demographic and clinical information

	Age	BMI	Age of onset	Duration of illness	Anorexia subtype	Comorbidities	Current medications	Previous treatment
Patient A	23	15.7	12	~12 years	Restrictive (purging)	Depression	Olanzapine, Diazepam and Fluoxetine	~12 years inpatient
Patient B	52	16.4	17	~35 years	Binge-purge	—	Fluoxetine	6 months daycare and ~3 years outpatient

and the Talarach coordinates $x = -45$, $y = 45$ and $z = 35$ (Fitzgerald *et al.*, 2009) in 5 s trains/55 s intervals at a frequency of 10 Hz, intensity of 110% MT delivering 1000 pulses over 20 min.

Baseline measures included height, weight, Eating Disorder Examination Questionnaire (EDE-Q) version 6 (Fairburn, 2009) and the 21-item Depression, Anxiety and Stress Scale (DASS-21) (Lovibond & Lovibond, 1995). These were repeated at post-treatment and at 1 month follow-up. Within sessions, following cue exposure to food stimuli (i.e. viewing a short film clip of people eating highly palatable foods), subjective experiences relating to the ED were assessed immediately before and after each rTMS session using 10-cm visual analogue scales (VAS). These VAS included measures of 'levels of anxiety', 'urge to restrict', 'feeling full' and 'feeling fat'.

Results

Patient A

Within-session measures

Data from the within-session VAS measures are presented in Figures 1a–d. There was a consistent drop in scores following each

application of rTMS. Additionally, scores reduced over the course of the treatment, beginning at between 6–8/10 and finishing at approximately 1/10 at completion.

Between-session measures

Patient A's weight, ED and mood outcomes are presented in Table 2. There was no substantial change in weight throughout the course of the 20 sessions, and at 1 month follow-up, Patient A had lost approximately 2 kg. At baseline, EDE-Q scores were indicative of severe ED psychopathology. Following the 20 rTMS sessions, total and EDE-Q subscales scores improved (with the exception of the eating subscale which remained unchanged), and at 1 month follow-up, this improvement continued, demonstrated by an EDE-Q total score below the cut-off (>2.80) for clinical significance (Mond *et al.*, 2008).

Patient A also demonstrated an improvement in mood. Prior to commencing treatment, DASS-21 scores were above the normative baseline of 13 (Henry & Crawford, 2005), and at completion of the 20 sessions, total DASS-21 score was below this with reductions across all three (depression, anxiety and stress) domains. One month following completion of the rTMS intervention, total

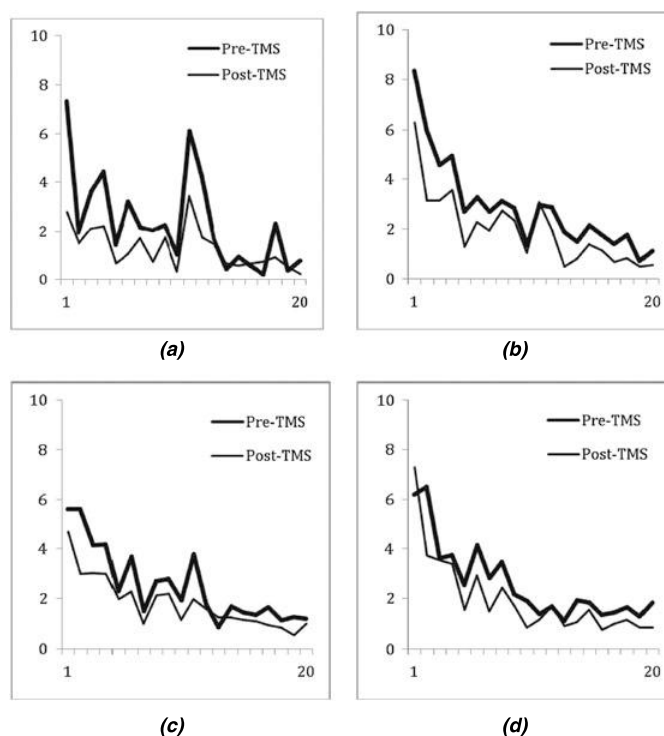


Figure 1. Patient A's within-session visual analogue scales scores. (a) Anxiety. (b) Urge to restrict. (c) Feeling full. (d) Feeling fat

Table 2 Between-session measures: Pre, post and 1 month follow up (FU) outcomes

		Patient A			Patient B		
		Pre	Post	1 month FU	Pre	Post	1 month FU
Weight (kg)		36.90	36.20	34.50	47.4	47.5	46.20
BMI		15.76	15.46	14.74	16.40	16.44	15.99
EDE-Q	Restraint	4.80	4.20	4.20	5.40	6.00	6.00
	Eating	2.60	2.60	2.00	3.80	1.40	1.00
	Shape	5.34	3.25	2.87	3.87	2.62	2.25
	Weight	4.40	2.00	1.60	3.40	3.80	4.20
	Total	4.29	3.01	2.67	4.12	3.46	3.36
DASS-21	Depression	4	2	6	10	11	7
	Anxiety	9	3	5	11	5	5
	Stress	10	6	7	19	7	9
	Total	23	11	18	40	23	21

DASS-21 score had increased above normal and across all three subscales, however, remained lower than individual baseline with the exception of the depression subscale.

Qualitative information

We gathered qualitative information from both Patient A and her care team surrounding any noticeable changes throughout the course of the treatment. Patient A did not experience or report any adverse symptoms/side effects of the rTMS treatment. Although Patient A said that she did not notice any major change to her eating behaviours, she did report feeling calmer, having a brighter mood, feeling 'better equipped to cope with things' and that she was more able to rationalize and accept things particularly in terms of changes to future treatment plans. Patient A's care team echoed this feedback, reporting her to be more logical, rational and less resistant to change.

Prior to and during the 20 rTMS sessions, Patient A had been on a nasal gastric feed and one-to-one observations. At completion of the rTMS treatment, she came off both interventions, and both Patient A and her care team reported that she found this very difficult. Consequently, Patient A reported an increase in vomiting behaviours, which is likely to have contributed to her weight loss of 2 kg at 1 month follow-up.

Patient B

Within-session measures

Data from the within-session VAS measures are presented in Figures 2a–d (with the exception of session 5 when VAS weren't collected due to time constraints; results from sessions 4 and 6 have been averaged for session 5). There was a downward trend in Patient B's anxiety scores following cue exposure within each session. Her urge to restrict remained unchanged and high (>9) both within sessions and throughout the course of the treatment, and whilst levels of feeling full and feeling fat reduced within some sessions, the pattern of change was inconsistent over the course of the treatment.

Between-session measures

Data relating to Patient B's weight, ED symptoms and mood are presented in Table 2. Weight remained unchanged throughout the course of treatment and dropped by 1 kg at 1 month follow-up. ED symptoms were initially indicative of severe ED pathology

as indexed by the EDE-Q, and mood scores on the DASS-21 were above normative baseline. Following the 19 rTMS sessions, both total EDE-Q and DASS-21 scores had improved and continued to do so at 1 month follow-up. Binge frequency remained the same (8 times per month) following the 19 rTMS sessions, however, reduced to 5 times per month at follow-up. Patient B also reported a reduction in both vomiting behaviour and laxative use. Initially, Patient B presented with 10 episodes of vomiting per month, which reduced to 8 following the 19 rTMS sessions and then 7 at follow-up. Patient B's laxative use improved similarly from a baseline frequency of 15 to 10 at completion, and further to 9 instances per month at follow-up.

Qualitative information

This was gathered from both Patient B and her husband regarding her progress throughout the treatment. Aside from the single report of dizziness/feeling dazed following one session, Patient B did not report any adverse symptoms/side effects of the rTMS. Patient B was very positive about this intervention, stating that it 'has done more for me than any other form of treatment'. She reported feeling calmer, having better control over her emotions and that she felt less motivated to engage in purging behaviours, describing them as 'less rewarding'. Patient B's husband reported improved mood, specifically the ability to cope with low moods, a reduction in purging behaviours and a noticeable increase in Patient B's determination to cease these. Both Patient B and her husband reported a significant change in her belief, hope and motivation towards recovery and wish for further rTMS sessions.

Discussion

Findings from both cases show that there was between-session improvement in both ED symptomatology and mood over the course of 19–20 sessions of neuronavigated rTMS, and that these changes persisted or even increased up to the 1 month follow-up. Although Patient A was receiving inpatient treatment at the time, she had carried out so for approximately 12 years prior, whereas Patient B received only antidepressant medication (but had no other concurrent form of treatment) in conjunction with the rTMS intervention. Because of the enduring (12 and 35 years) and treatment-resistant nature of AN in both cases, we believe a

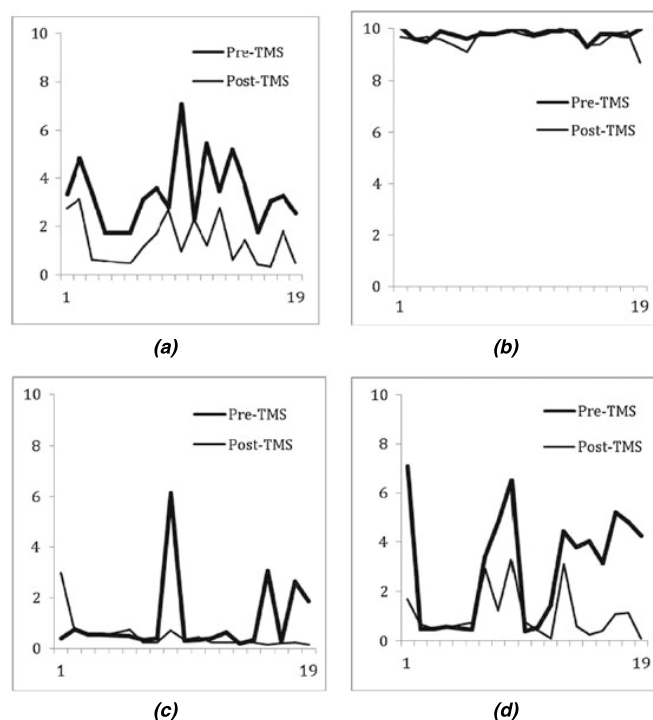


Figure 2. Patient B's within-session visual analogue scales scores. (a) Anxiety. (b) Urge to restrict. (c) Feeling full. (d) Feeling fat

placebo response is unlikely and that the symptom improvements seen are, at least in part, a result of the rTMS treatment.

We can only speculate on the potential mechanisms of action of rTMS in these two very severe and enduring AN cases. Firstly, they may have resulted from changes to dorsal neural-circuits responsible for executive functions, leading to improved cognitive flexibility and self-regulation, as has been suggested by rTMS findings in patients with treatment-resistant depression (Kedzior, Rajput, Price, Lee, & Martin-Iverson, 2012). Alternatively, the combination of rTMS and cue exposure included in the current protocol may have contributed to the reduction in ED-related anxieties via an effect on extinction learning, which might not have been achieved with either rTMS or exposure therapy alone (Baek, Chae, & Jeong, 2012). Our study only included short-term follow-up, but the fact that—even in these patients with very entrenched illnesses—changes persisted is in line with animal studies that have found long-lasting effects in neuroplasticity following repeated sessions of high frequency rTMS (Gersner, Kravetz, Feil, Pell, & Zangen, 2011).

The lack of weight gain, and in fact slight weight loss at follow up in both patients, cannot be ignored as weight gain is an

obvious treatment goal in this patient group. However, the natural history of enduring AN in both cases demonstrates that changes in weight require both time and significant improvements to patients' psychological state. Both patients reported noticeable changes to factors such as motivation, coping ability and affective regulation during the course of rTMS sessions; therefore, perhaps with time and concurrent psychotherapy these improvements could be utilized to encourage weight gain.

So far, evidence for the potential therapeutic benefit of rTMS in AN has been limited to one other case report (Kamolz et al., 2008) and our small pilot study demonstrating short-term effects of rTMS on AN symptoms (Van den Eynde et al., 2011). The two cases reported here, add to this sparse literature by providing preliminary evidence for feasibility, acceptability and some suggestion of efficacy of therapeutic rTMS, given converging positive findings from within-session and between-session outcomes and qualitative reports. As a next step, larger case series of therapeutic rTMS in AN are warranted to explore its suitability for different target populations (e.g. restricting or binge-purge type AN) or target symptoms (e.g. ED symptoms or symptoms of comorbid disorders, such as severe depression, obsessive-compulsive disorder

or post-traumatic stress syndrome, that are known to respond to rTMS treatment). In the longer term, large scale high quality RCTs of therapeutic rTMS in patients with AN are needed, together with research into different rTMS protocols for AN and for ED in general, utilizing different types of stimulation (high or low frequencies, unilateral or bilateral) or different stimulation sites. Such research will help to further clarify the neural-circuitry underpinning different AN symptoms, in addition to establishing the therapeutic potential of neuromodulation techniques in treating ED. Such tools, if proved beneficial, could exist as viable adjuncts to existing psychotherapy interventions.

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Appendix B: Copy of ethical approval



Health Research Authority

NRES Committee London - City & East
Bristol Research Ethics Committee Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 01173421386
Facsimile: 01173420445

02 November 2012

Ms Jessica McClelland
Institute of Psychiatry P059
De Crespigny Park, London
SE58AF

Dear Ms McClelland,

Study title: An integrated study of (a) an experimental sham-controlled randomised trial of one session of repetitive Transcranial Magnetic Stimulation (rTMS) and (b) a 20 session feasibility case series of therapeutic rTMS in outpatients with Anorexia Nervosa (AN).

REC reference: 12/LO/1525

Thank you for your letter of 23 October 2012, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a sub-committee of the REC. A list of the sub-committee members is attached.

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, 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).

Non-NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

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).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Advertisement	Study Poster: Version 1	02 August 2012
Covering Letter		28 August 2012
Covering Letter		23 October 2012
Evidence of insurance or indemnity	AJ Gallagher: Period 01.08.2012 to 01.08.2013	30 July 2012
GP/Consultant Information Sheets	Single Session: Version 1	02 August 2012
GP/Consultant Information Sheets	20 Sessions: Version 1	02 August 2012
Interview Schedules/Topic Guides	Single Session: Version 1	02 August 2012
Interview Schedules/Topic Guides	20 Sessions: Version 1	02 August 2012
Investigator CV	Jessica McClelland	29 August 2012
Investigator CV	Ulrike Schmidt	
Other: Peer Review Letter		
Participant Consent Form: Single Session	1	02 August 2012
Participant Consent Form: 20 Sessions	1	02 August 2012
Participant Consent Form: Consent Form (Case Series)	2	23 October 2012
Participant Consent Form: Consent Form (RCT)	2	23 October 2012
Participant Information Sheet: Single Session	1	02 August 2012
Participant Information Sheet: 20 Sessions	1	02 August 2012
Participant Information Sheet: (Case Series)	2	23 October 2012
Participant Information Sheet: (RCT)	2	23 October 2012

Protocol	1	02 August 2012
REC application		28 August 2012
Response to Request for Further Information		23 October 2012

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

12/LO/1525	Please quote this number on all correspondence
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With the Committee's best wishes for the success of this project

Yours sincerely,



Dr Arthur T. Tucker
Chair

Email: Ubh-tr.CityandEastREC@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Jenny Liebscher, South London and Maudsley NHS Foundation Trust
R&D Office

Appendix C: Participant information sheets

Appendix C.1 Information sheet for the randomised control trial



South London and Maudsley **NHS**
NHS Foundation Trust

Eating Disorders Outpatients Unit
Maudsley Hospital
Denmark Hill
London SE5 8AZ

☎ 0207 848 0183
📠 020-3228 2358

Research Ethics Committee Reference Number: 12/LO/1525
Participant Information Sheet Version 2
Date: 23 October 2012

An Investigation into the Effects of Repetitive Transcranial Magnetic Stimulation (rTMS) in Anorexia Nervosa (single session)

Participant Information Sheet

Dear ,

We would like to invite you to take part in a study exploring the brain processes thought to underlie and drive preoccupation with food, eating, body weight and shape in people with Anorexia Nervosa. Before you decide to take part in the study, you need to understand why the research is being done and what your participation would involve if you decided to take part. Please take the time to read the following information carefully and do not hesitate to ask us if there is anything that you are unsure of or if you would like more information. Please take your time in deciding whether or not you would like to participate.

Background and purpose of the study

Psychological treatments are effective for some but not all people with anorexia nervosa. Therefore, there is an ongoing need for the development of new treatments. There is ample evidence that suggests that frontal areas of the brain play a role in the development and maintenance of eating disorders, including anorexia nervosa. Stimulating these brain areas to improve their functioning is therefore believed to have the potential to reduce eating disorder symptoms. A technique that is capable of stimulating specific brain areas is repetitive Transcranial Magnetic Stimulation (rTMS) which involves the delivery of magnetic waves to the brain by holding a coil to the skull. This procedure is widely used in research and is being applied in clinical settings.

In a previous pilot study, we found that a single session of rTMS lead to a reduction in some of the core symptoms of anorexia and bulimia. In this study

we aim to further investigate the short-term effects of a single session of rTMS in women who suffer from anorexia nervosa. In particular we are interested in its effect on thinking processes and emotions that underlie the preoccupation with food, eating, weight and body shape. In the long-term, this may help us develop improved treatments for anorexia nervosa. Your participation in this study would help to achieve this objective. In total, 64 people with anorexia nervosa or related disorders will be included in this study.

Why are you invited to participate and do you have to participate?

To be eligible to participate in the study, individuals must have a current diagnosis of anorexia nervosa or an associated disorder (e.g. having eating problems and a body mass index of less than 18.5kg/m²). It is important to tell us if you have any metal in your body (for example, artificial hip joints, pacemakers, clips) and you must be able to sit upright in a comfortable chair for up to 1 hour. If you are pregnant you will not be able to participate in this study. You will be requested to inform the researcher of this information.

You do not have to take part in this study. It is up to you to decide whether you wish to participate or not. If you decide to participate, we will then ask you to sign a consent form to show that you have agreed to take part. You are free to withdraw at any time, without giving a reason. It is of importance for you to know that, if you decide not to take part in this study or to withdraw from the study, this will not affect the care you receive.

What will my participation involve me doing?

Your participation will involve you having a MRI brain scan and a real or sham (placebo) rTMS session. You will also be required to complete a number of questionnaires (assessing mood and eating habits), ratings in relation to different food types and neuropsychological tasks (brain puzzles). We will also collect saliva samples to measure cortisol (this is a stress hormone).

There is no need for special preparation but you will be asked to remove any metallic jewellery or other items, which would be sensitive to magnetic fields. You will be asked to sit upright in a comfortable chair and wear small headband which helps locate the rTMS coil accurately. The stimulation is applied using a special coil held by the researcher just touching your head.

What will happen on the day?

Participation in this study involves of a full day's attendance (9am – 5pm). The day's proceedings are detailed below:

- MRI brain scan in the morning (30-60 minutes)
- Break (2-3 hours)
- Stimulation session involving:
 - Questionnaires, tasks, food ratings and saliva samples (1 hour)
 - Stimulation session of real/sham rTMS (45 minutes)
 - Questionnaires, tasks, food ratings and saliva samples (1 hour)

After completion of the above tasks you will be free to leave. A researcher will call you the next day for a 24hour follow up call which should last no longer than 15 minutes.

In order to detect the effects of rTMS not all participants will receive rTMS, that is half of the participants will receive a sham (placebo) rTMS stimulation. This will be a random allocation and you will not be aware of which (real or sham) stimulation you receive. In the 24hour follow up phone call you will be asked to guess which stimulation you think you received, and then you will be informed which stimulation you actually received. If you are randomly allocated to receive the sham stimulation session and you would like to experience a session of real rTMS, arrangements will be made for you to do so at a later date.

Expenses and payments

As a participant you will be given £50 as reimbursement for your time, efforts and travel.

What is expected from you?

We would expect you to attend the session as scheduled and to advise us immediately, if for any reason you suddenly find yourself unable to attend a previously scheduled session (so we can try to find someone else to take the vacant slot).

Please let us know of any health problem that has developed since you enrolled for the study. Further, we would ask you to let us know of any new medication or change in medication whilst you are taking part in the study.

What are the possible disadvantages and risks of participating in this study?

There are no risks of participating in this study. You may however find the procedure slightly uncomfortable. In that case, remember, you are free to withdraw from the study at any time without the need to justify your decision. If you decide to withdraw from the study, this will not affect the treatment you receive.

The most common side effect of rTMS is mild discomfort in the scalp beneath the magnetic coil. Some people suffer a mild headache, which is treatable with simple painkillers such as paracetamol. The most serious side effect, but a very rare one (less than 1% likelihood in healthy people), is the production of an epileptic seizure. We will complete a safety questionnaire to exclude circumstances that would be associated with an increased risk for a seizure. The magnetic coil makes a series of loud clicks during the treatment. These are not loud enough to harm your hearing, but you will be asked to wear earplugs as a precaution.

Will you benefit from taking part?

This study is not intended to help any individual participant but the information we get may help improve the treatment of people with anorexia. You will be offered the opportunity to be informed about your individual results once the

data for all participants has been collected. If you want to have written feedback of the study findings, you can contact the researcher (contact details below) for a summary. The results of the study will be sent to a medical journal for publication. Your participation in the study will, of course, not be disclosed.

What if new information becomes available?

This is highly unlikely to occur within the time frame (8 hours) of this study. However if it does, you will be informed immediately.

What if you don't want to carry on with the study?

If you withdraw from the study we will ask your permission to use any data collected up to the time of your withdrawal.

What if there is a problem?

If you have a concern about any aspects of this study, you should ask to speak to the researchers who will do their best to answer your questions (Ms Jessica McClelland – Tel: 0207 848 0183 Email: jessica.mcclelland@kcl.ac.uk). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the South London and Maudsley NHS Foundation Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will your participation be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The data from this study will be anonymised and coded. These electronic data will be stored on University computers, which are all password protected. Paper data will be stored in locked cupboards at the Eating Disorders Unit at the Institute of Psychiatry. Only researchers involved in this study and regulatory authorities will have access to the data. All information which is collected during the course of the research will be kept strictly confidential according to the Data Protection Act 1998.

Who is organising and funding this research?

This study will be funded by the Eating Disorders Section at the Institute of Psychiatry, Kings College London. The researchers in the study will not be paid for including you in this study.

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 safety, rights, wellbeing and dignity.

This study has been reviewed and given favourable opinion by the Joint SLAM NHS and Institute of Psychiatry Research Ethics Committee.

Further information about the study and contact details:

General information about this research project can be obtained from Miss Jessica McClelland, Section of Eating Disorders, Institute of Psychiatry at the Maudsley (Tel: 0207 848 0183 or Email: jessica.mcclelland@kcl.ac.uk).

If you have a concern about any aspects of this study, you should ask to speak to the researchers who will do their best to answer your questions (Tel: 0207 848 5608). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital. The Patient Advice and Liaison Service would be able to assist you (Tel: 0800 7312864 or email: pals@slam.nhs.uk).

Appendix C.2 Information sheet for the therapeutic case series



South London and Maudsley 
NHS Foundation Trust

Eating Disorders Outpatients Unit
Maudsley Hospital
Denmark Hill
London SE5 8AZ

☎ 0207 848 0183
📠 020-3228 2358

Research Ethics Committee Reference Number: 12/LO/1525
Participant Information Sheet Version 3
Date: 9 July 2013

An Investigation into the Effects of Repetitive Transcranial Magnetic Stimulation (rTMS) in Anorexia Nervosa (20 sessions)

Participant Information Sheet

Dear ,

We would like to invite you to take part in a study exploring the brain processes thought to underlie and drive preoccupation with food, eating, body weight and shape in people with Anorexia Nervosa. Before you decide to take part in the study, you need to understand why the research is being done and what your participation would involve if you decided to take part. Please take the time to read the following information carefully and do not hesitate to ask us if there is anything that you are unsure of or if you would like more information. Please take your time in deciding whether or not you would like to participate.

Background and purpose of the study

Psychological treatments are effective for some but not all people with anorexia nervosa. Therefore, there is an ongoing need for the development of new treatments. There is ample evidence that suggests that frontal areas of the brain play a role in the development and maintenance of eating disorders, including anorexia nervosa. Stimulating these brain areas to improve their functioning is therefore believed to have the potential to reduce eating disorder symptoms. A technique that is capable of stimulating specific brain areas is repetitive Transcranial Magnetic Stimulation (rTMS) which involves the delivery of magnetic waves to the brain by holding a coil to the skull. This procedure is widely used in research and is being applied in clinical settings.

In a previous pilot study, we found that a single session of rTMS lead to a reduction in some of the core symptoms of anorexia and bulimia. In this study

we aim to further investigate and substantiate the effects of rTMS in women who suffer from anorexia nervosa, by offering 20 sessions of rTMS over a 4-6 week period.

In particular we are interested in the effect of rTMS on thinking processes and emotions that underlie the preoccupation with food, eating, weight and body shape. In the long-term, this may help us develop improved treatments for anorexia nervosa. Your participation in this study would help to achieve this objective. In total, 10 people with anorexia nervosa or related disorders will be included in this study.

Why are you invited to participate and do you have to participate?

To be eligible to participate in the study, individuals must have a current diagnosis of anorexia nervosa or an associated disorder (e.g. having eating problems and a body mass index of less than 18.5kg/m²). It is important to tell us if you have any metal in your body (for example, artificial hip joints, pacemakers, clips) and you must be able to sit upright in a comfortable chair for up to 1 hour. If you are pregnant you will not be able to participate in this study. You will be requested to inform the researcher of this information.

You do not have to take part in this study. It is up to you to decide whether you wish to participate or not. We will describe the study and go through this information sheet, which we will then give to you. If you decide to participate, we will then ask you to sign a consent form to show that you have agreed to take part. You are free to withdraw at any time, without giving a reason. It is of importance for you to know that, if you decide not to take part in this study or to withdraw from the study, this will not affect the care you receive.

What will my participation involve me doing?

In order to take part in this study, you will have already participated in the single session rTMS trial and had a structural brain scan (MRI). This longer, therapeutic styled study employs a similar format, however will require you to be able to commit to 20 sessions of rTMS spread over a 4-6 week period. A minimum of three, maximum of five visits per week is required. A number of initial measurements will be taken on your first visit, including height and eating related attitudes and behaviours and you will be weighed on a weekly basis. All other sessions will just involve questionnaires before and after stimulation. The rTMS is done simultaneously with watching a short film clip of people eating and body image related scenes. A typical session would last 30-50minutes.

There is no need for special preparation but you will be asked to remove any metallic jewellery or other items, which would be sensitive to magnetic fields. It is important to tell us if you have any metal in your body (for example, artificial hip joints, pacemakers, clips). You will be asked to sit upright in a comfortable chair and wear small headband which helps locate the coil accurately. The stimulation is applied using a special coil held by the researcher just touching your head and the procedure lasts about 20minutes.

Expenses and payments

This study is set up as an adjunctive treatment trial, therefore no payment for participation will be given. However, travel expenses may be met in some circumstances.

What is expected from you?

We would expect you to attend the 20 sessions as scheduled and to advise us immediately, if for any reason you suddenly find yourself unable to attend a scheduled session.

Please let us know of any health problem that has developed since you enrolled for the study. Further, we would ask you to let us know of any new medication or change in medication whilst you are taking part in the study.

What are the possible disadvantages and risks of participating in this study?

There are no risks of participating in this study. You may however find the procedure slightly uncomfortable. In that case, remember, you are free to withdraw from the study at any time without the need to justify your decision. If you decide to withdraw from the study, this will not affect the treatment you receive.

The most common side effect of rTMS is mild discomfort in the scalp beneath the magnetic coil. Some people suffer a mild headache, which is treatable with simple painkillers such as paracetamol. The most serious side effect, but a very rare one (less than 1% likelihood in healthy people), is the production of an epileptic seizure. In addition, we will complete a safety questionnaire to exclude circumstances that would be associated with an increased risk for a seizure. The magnetic coil makes a series of loud clicks during the treatment. These are not loud enough to harm your hearing, but you will be asked to wear earplugs as a precaution.

If you are pregnant you will not be able to participate in this study due to the effects of MRI scanning on unborn children. You will be requested to inform the researcher of this information.

Will you benefit from taking part?

This study is intended to improve symptoms of anorexia, therefore benefit in relation to an individual's eating disorder related symptoms is expected. Additionally, if you want to have written feedback of the study findings, you can contact the researcher (contact details below) for a summary.

What if there is a problem?

Any concern or complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in part 2 of this information sheet.

Will your participation be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The data from this study will be anonymised and coded. These electronic data will be stored on University computers, which are all password protected. Paper data will be stored in locked cupboards at the Eating Disorders Unit at the Institute of Psychiatry. Only researchers involved in this study and regulatory authorities will have access to the data. All information which is collected during the course of the research will be kept strictly confidential according to the Data Protection Act 1998.

What if new information becomes available?

This is highly unlikely to occur within the time frame of this study however if it does, you will be informed immediately.

What if you don't want to carry on with the study?

If you withdraw from the study we will ask your permission to use any data collected up to the time of your withdrawal.

What if there is a problem?

If you have a concern about any aspects of this study, you should ask to speak to the researchers who will do their best to answer your questions (Ms Jessica McClelland – Tel: 0207 848 0183 Email: jessica.mcclelland@kcl.ac.uk). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the South London and Maudsley NHS Foundation Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

What will happen to the results of the research study?

You will be offered the opportunity to be informed about your individual results once the data for all participants have been collected. The results of the study will be sent to a medical journal for publication. Your participation in the study will, of course, not be disclosed.

Who is organising and funding this research?

This study will be funded by the Eating Disorders Section at the Institute of Psychiatry, Kings College London. The researchers in the study will not be paid for including you in this study.

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 safety, rights, wellbeing and dignity.

This study has been reviewed and given favourable opinion by the Joint SLAM NHS and Institute of Psychiatry Research Ethics Committee.

Further information about the study and contact details:

General information about this research project can be obtained from Miss Jessica McClelland, Section of Eating Disorders, Institute of Psychiatry at the Maudsley (Tel: 0207 848 0183 or Email: jessica.mcclelland@kcl.ac.uk).

If you have a concern about any aspects of this study, you should ask to speak to the researchers who will do their best to answer your questions (Tel: 0207 848 0183). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital. The Patient Advice and Liaison Service would be able to assist you (Tel: 0800 7312 864 or email: pals@slam.nhs.uk).

Appendix D: Participant consent forms

Appendix D.1 Consent form for the randomised control trial



South London and Maudsley 
NHS Foundation Trust

Eating Disorders Outpatients Unit
Maudsley Hospital
Denmark Hill
London SE5 8AZ

☎ 0207 848 0183

☎ 020-3228 2358

Research Ethics Committee Reference Number: 12/LO/1525

Consent Form Version 2

Date: 23 October 2012

Centre Number:

Study Number:

Patient ID:

CONSENT FORM

An Investigation of the Effects of Repetitive Transcranial Magnetic Stimulation (rTMS) in Anorexia Nervosa (single session)

Name of Researcher:

1. I have read the information sheet dated..... version.....
For the above study. I have had the opportunity to consider the
information and ask questions
2. 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.
3. I consent that relevant sections of my medical notes and data
collected during this study may be looked at by the research team
involved in the study where it is relevant to my taking part in this
research. I give permission for these individuals to have access to my
records.
4. I consent / do not consent (please circle) to my GP being informed of
my participation in this study. (Please note: you are still eligible to
participate in the study even if you do not want your GP informed of
your involvement).

Consent Form (RCT) Version 2 – 23/10/2012

5. I know that if I would like to, I can contact the research team and request a written summary of findings of the study.

6. I agree to take part in the above study.

_____	_____	_____
Participants name	Date	Signature

I have explained the study to the participant and have answered their questions honestly and fully.

_____	_____	_____
Name of person Taking consent	Date	Signature

Enquiries:
Jessica McClelland
P095, Section of Eating Disorders,
Institute of Psychiatry,
De Crespigny Park,
London, SE5 8AF,

Phone: 0207 848 0183

Email: jessica.mcclelland@kcl.ac.uk

Appendix D.2 Consent form for the therapeutic case series



South London and Maudsley 
NHS Foundation Trust

Eating Disorders Outpatients Unit
Maudsley Hospital
Denmark Hill
London SE5 8AZ

☎ 0207 848 5608

☎ 020-3228 2358

Research Ethics Committee Reference Number: 12/LO/1525
Consent Form Version 2
Date: 23 October 2012

Centre Number:
Study Number:
Patient ID:

CONSENT FORM

An Investigation of the Effects of Repetitive Transcranial Magnetic Stimulation (rTMS) in Anorexia Nervosa (20 sessions)

Name of Researcher:

1. I have read the information sheet dated..... version.....
For the above study. I have had the opportunity to consider the information and ask questions
2. 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.
3. I consent that relevant sections of my medical notes and data collected during this study may be looked at by the research team involved in the study where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
4. I consent / do not consent (please circle) to my GP being informed of my participation in this study. (Please note: you are still eligible to participate in the study even if you do not want your GP informed of your involvement).

Consent Form (case series) Version 2 – 23/10/2012

5. I know that if I would like to, I can contact the research team and request a written summary of findings of the study.

6. I agree to take part in the above study.

_____	_____	_____
Participants name	Date	Signature

I have explained the study to the participant and have answered their questions honestly and fully.

_____	_____	_____
Name of person Taking consent	Date	Signature

Enquiries:
Jessica McClelland
P095, Section of Eating Disorders,
Institute of Psychiatry,
De Crespigny Park,
London, SE5 8AF,

Phone: 0207 848 5608

Email: jessica.mcclelland@kcl.ac.uk

Appendix E: Screening/baseline-1 documents

Appendix E.1 Demographic information questionnaire

1. Have you been diagnosed with an eating disorder?	YES	NO
... what is your current diagnosis/symptomatology?		
...restrictive, binge/purge, excessive exercise?		
2. How long have you been suffering from this eating disorder?		
3. Have you been diagnosed with another psychiatric disorder(s)?	YES	NO
..... if YES which one and when? (eg depression, anxiety, panic, PTSD,OCD)		
4. Have you had any significant health problems in past 6 months?	YES	NO
..... if YES please provide more details? (eg diabetes, asthma, chronic pain, cardiovascular/heart problems?)		
5. Have you ever had any neurological disease (eg stroke), brain or eye injury or any brain surgery?	YES	NO
..... if YES please provide more details?		
6. Do you experience regular headaches, migraines, dizzy or fainting spells, double or blurred vision, numbness or tingling, or problems with balance?	YES	NO
..... if YES please provide more details?		
7. Have you had blood tests done in the past month?	YES	NO
....if YES where and were there any abnormal results?		

8. Do you smoke more than 10 cigarettes/day?	YES	NO
9. How much alcohol do you drink? if YES what type? (eg. wine, beer, spirits)days/wkdrinks/day	
10. Do you take drugs?	YES	NO
11. Are you currently taking any medication?if YES which one and for how long?	YES	NO
12. Are you currently receiving any psychological/psychiatric treatment? ...if YES are you happy for us to inform them of your participation? ...if YES please provide their name and contact details Name: Phone: Address:	YES YES	NO NO
13. Do you have a current GP? ...if YES are you happy to provide their details in case of an emergency? Name: Phone: Address:	YES	NO
13. Are you pregnant?	YES	NO
14. Within the past 6 months have you had any suicidal ideation? ...if YES, have you made any suicide attempts within the past 6 months?	YES YES	NO NO

Appendix E.2 Eating Disorder Diagnostic Scale (EDDS)

Over the past 3 months...

	Not at all		Slightly		Moderately		Extremely	
1. Have you felt fat?	0	1	2	3	4	5	6	
2. Have you had a definite fear that you might gain weight or become fat?	0	1	2	3	4	5	6	
3. Has your weight influenced how you think about (judge) yourself as a person?	0	1	2	3	4	5	6	
4. Has your shape influenced how you think about (judge) yourself as a person?	0	1	2	3	4	5	6	

5. During the past **6 months** have there been times when you felt you have eaten what other people would regard as an unusually large amount of food (e.g., a quart of ice cream) given the circumstances? **YES** **NO**

6. During the times when you ate an unusually large amount of food, did you experience a loss of control (feel you couldn't stop eating or control what or how much you were eating)? **YES** **NO**

7. How many **days per week** on average over the **past 6 months** have you eaten an unusually large amount of food and experienced a loss of control?

0 1 2 3 4 5 6 7

8. How many **times per week** on average over the **past 3 months** have you eaten an unusually large amount of food and experienced a loss of control?

0 1 2 3 4 5 6 7 8 9 10 11
12 13 14

During these episodes of overeating and loss of control did you...

9. Eat much more rapidly than normal? YES NO

10. Eat until you felt uncomfortably full? YES NO

11. Eat large amounts of food when you didn't feel physically hungry?
YES NO

12. Eat alone because you were embarrassed by how much you were eating?
YES NO

13. Feel disgusted with yourself, depressed, or very guilty after overeating?
YES NO

14. Feel very upset about your uncontrollable overeating or resulting weight gain?
YES NO

15. How many times per week on average over the past 3 months have you made yourself vomit to prevent weight gain or counteract the effects of eating?

0 1 2 3 4 5 6 7 8 9 10 11
12 13 14

16. How many times per week on average over the past 3 months have you used laxatives or diuretics to prevent weight gain or counteract the effects of eating?

0 1 2 3 4 5 6 7 8 9 10 11
12 13 14

17. How many times per week on average over the past 3 months have you fasted (skipped at least 2 meals in a row) to prevent weight gain or counteract the effects of eating?

0 1 2 3 4 5 6 7 8 9
10 11 12 13 14

18. How many times per week on average over the past 3 months have you engaged in excessive exercise specifically to counteract the effects of overeating episodes?

0 1 2 3 4 5 6 7 8 9
10 11 12 13 14

19. How much do you weigh? If uncertain, please give your best estimate.

_____ lbs.

20. How tall are you? _Please specify in inches (5 ft.= 60 in.)

_____ in.

21. Over the past **3 months**, how many menstrual periods have you missed?

0 1 2 3 n/a

22. Have you been taking birth control pills during the past **3 months**?

YES NO

Appendix E.3 Structured clinical interview for DSM-IV axis disorders (SCID)

Now I want to ask you some specific questions about problems you may have had. We'll go into more detail about them later.

RESPOND TO POSITIVE RESPONSES WITH: We'll talk more about that later.

1. Was there ever a period in your life when you drank

too much and:

- a) alcohol caused problems for you (probe:
controlling drinking, work, family, friends,
financially) or;
- b) someone else objected to your drinking
or thought it was a problem for you?

1 2 3

If yes to a) or b) Circle Yes on E.1 and
assess for alcohol problems

2. Have you ever regularly or frequently used street

drugs and:

- a) street drugs caused problems for you (probe:
controlling drinking, work, family, friends,
financially) or;
- b) someone else objected to you taking street drugs
or thought street drugs were a problem for you?

1 2 3

If yes to a) or b) Circle Yes on E.10
and assess for substance abuse

3. In the last six months, have you been particularly
nervous or anxious? Do you worry about a lot about
bad things might happen? During the last 6 months
would you say that you have been worrying more
days than not?

1 2 3

If 'yes' circle yes on F.31. and assess for
assess for G.A.D

1 = absent or false

2 = subthreshold

3 = threshold or true

4. Have you ever had periods when you were feeling depressed or down most of the day nearly every day? Or a time when you lost interest in things that you usually enjoyed?	1	2	3	If 'yes' circle yes on A.1. and assess for Major Depressive Episode (current then past)
5. Have you ever felt so bad that you thought about hurting yourself? Or had times when you've thought about death or even wished you were dead?	1	2	3	Screeners only – If 'yes' assess risk to
6. Have you ever had a panic attack. When you suddenly felt frightened or anxious or suddenly developed a lot of physical symptoms?	1	2	3	If 'yes' circle yes on F.1. and assess for panic disorder
7. Were you ever afraid of going out of the house alone, being in crowds, standing in a line, or travelling on buses or trains?	1	2	3	If 'yes' circle yes on F.7. and assess for agoraphobia
8. Is there anything that you have been afraid to do or felt uncomfortable doing in front of other people, like speaking, eating or writing?	1	2	3	If 'yes' circle yes on F.11. and assess for social anxiety
9. Are there any other things that you have been Especially afraid of like flying, seeing blood, injections, heights, closed places, or certain kinds of animals or insects?	1	2	3	If 'yes' circle yes on F.16. and assess for specific phobias

1 = absent or false

2 = subthreshold

3 = threshold or true

10. Have you ever been bothered by thoughts that didn't make any sense and kept coming back to you even when you tried not to have them?	1 2 3
	If 'yes' circle yes on F.20. and assess for obsession

IF NOT SURE WHAT IS MEANT: Thoughts like hurting someone even though you really didn't want to or being contaminated by germs or dirt.

11. Was there ever anything that you had to do over and over again and couldn't resist doing, like washing your hands again and again, counting up to a certain number, or checking something several times to make sure that you'd done it right	1 2 3
	If 'yes' circle yes on F.21. and assess for compulsions

12. Have you ever felt so good, or high, or hyper, that other people thought you were not your normal self?	1 2 3
	If 'yes' circle yes on A18. and assess for manic episodes (current then past)

13. Sometimes things happen to people that are extremely upsetting – things like being in a life threatening situation like a major disaster, very serious accident or fire; being physically assaulted or raped; seeing another person killed or dead, or badly hurt, or hearing about something horrible that has happened to someone you are close to. At any time during your life, have any of these kinds of things happened to you?	1 2 3
	1: NO 2: Yes, but not in the past 12 mths 3: Yes, in the past 12 mths

What traumatic event or events have you experienced?
(Anything else?)

1 = absent or false

2 = subthreshold

3 = threshold or true

Sometimes after experiencing very upsetting events like this/these, people have psychological or emotional reactions, such as nightmares, thoughts they can't get out of their heads, or trying to avoid anything that reminds them of the event. Did you ever have any reactions like that after (it/ that event/ any of those events) TRAUMATIC EVENT?

(IF YES: Has that happened in the past 12 months?)

- | | | | |
|---|---|---|---|
| 14. Have you ever had a time when you weighed much less than other people thought you ought to weigh? | 1 | 2 | 3 |
| 15. Have you often had times when your eating was out of control? | 1 | 2 | 3 |
| 16. Some people are very bothered by the way that they look, aside from your weight and shape has this ever been a problem for you? | 1 | 2 | 3 |
| | If 'yes' circle yes on G13. and assess for BDD | | |
| 17. Now I am going to ask you about some unusual experiences that people sometimes have. Has it ever seemed like people were talking about you or taking special notice of you? Or have you ever heard things that other people could not see or seen things that other people could not see? | 1 | 2 | 3 |
| | Screener only – If 'yes' assess risk to self/others | | |

Use the following PSYCHOTIC screening questions at your own discretion

- | | | | |
|---|---|---|---|
| What about anyone going out of their way to give you a hard time, or trying to hurt you? | 1 | 2 | 3 |
| Have you ever felt that you were especially important in some way, or that you had special powers to do things that other people couldn't do? | 1 | 2 | 3 |
| Have you ever felt that something was very wrong with you physically even though your doctor said nothing was wrong...like you had cancer or some other terrible disease? | 1 | 2 | 3 |
| Were you convinced? Or did you think this could have been your imagination? | | | |

Appendix E.4 Centre for Neuroimaging Science MRI safety screening

Centre for Neuroimaging Sciences		MRI REQUEST FORM		South London and Maudsley NHS Foundation Trust	
PLEASE USE BLOCK CAPITALS TO COMPLETE THE FORM				Please Circle	
Surname		Forenames		Mr/Mrs/Miss/Ms	
Address		Ward			
NHS number		Hospital number			
Sex M / F		Date of Birth		Phone No	
GP details					
AREA OF MRI: HEAD/MRA/SPINE (cervical/thoracic/lumbar)			Check List (please circle)		
Indication:			Pacemaker? Y/N		
.....			Vascular Clips? Y/N		
.....			Metal in Eyes? Y/N		
.....			Is Subject Pregnant? Y/N		
.....			Is Subject Claustrophobic? Y/N		
.....			Does Subject have impaired Hearing? Y/N		
.....			Does Subject have Impaired Eyesight Y/N		
Relevant Medical History /Additional Information			For further advice on foreign bodies or other MR safety information please contact Extn 83084 or email askcns@iop.kcl.ac.uk		
.....					
.....					
.....					
ICD Code (if known).....IQ / NART			Left School with no qualifications Y		
Age of onset of Current Symptoms.....			Left School with qualifications Y		
Age of onset of First Symptoms.....			Left School post higher education Y		
Family History of Psychiatric Illness Y Y N Y DK Y					
Possible Dementia Y Y N Y DK Y			MMSE score.....		
Past History of Head Trauma Requiring Hospitalisation Y Y N Y DK Y					
Other disorder (please specify).....					
Symptoms (current or most recent episode)					
Hallucinations Y Y N Y DK Y			History of Alcohol abuse Y Y N Y DK Y		
Delusions Y Y N Y DK Y			History of Drug Abuse Y Y N Y DK Y		
Thought disorder Y Y N Y DK Y			Autism spectrum:		
Thought broadcasting Y Y N Y DK Y			Social Y Y N Y DK Y		
Withdrawal Y Y N Y DK Y			Repetitive Y Y N Y DK Y		
Insertion Y Y N Y DK Y			Communicative Y Y N Y DK Y		
Elevated Mood Y Y N Y DK Y			Symptoms.....		
Negative mood Y Y N Y DK Y			Learning disability Y Y N Y DK Y		
Anxiety/Panic Y Y N Y DK Y			Inattentiveness Y Y N Y DK Y		
PTSD Y Y N Y DK Y			Overactivity Y Y N Y DK Y		
			Impulsiveness Y Y N Y DK Y		
Research	Protocol Name	Contact Person	P.I. on Ethics Approval	Project Grant Holder	Date
Clinical	Hospital/Ward	Consultant	Contact Telephone Number	Directorate	Date
Print Name		Signature			

Appendix E.5 Transcranial magnetic stimulation adult safety screen

Transcranial Magnetic Stimulation[†] (TMS) Adult Safety Screen

Name:
Date:
Age:

Please answer the following:

Are you right handed? ☐Yes ☐No

Have you ever:

Had an adverse reaction to TMS? ☐Yes ☐No

Had a seizure? ☐Yes ☐No

Had an electroencephalogram (EEG)? ☐Yes ☐No

Had a stroke? ☐Yes ☐No

Had a serious head injury (include neurosurgery)? ☐Yes ☐No

Do you have any metal in your head (outside the mouth)
such as shrapnel, surgical clips, or fragments from welding
or metalwork? ☐Yes ☐No

Do you have any implanted devices such
as cardiac pacemakers, medical pumps, or intracardiac lines? ☐Yes ☐No

Do you suffer from frequent or severe headaches? ☐Yes ☐No

Have you ever had any other brain-related condition? ☐Yes ☐No

Have you ever had any illness that caused brain injury? ☐Yes ☐No

Are you taking any medications? ☐Yes ☐No

If you are a woman of childbearing age, are you sexually
active, and if so, are you *not using* a reliable method of birth control?
☐Yes ☐No

Does anyone in your family have epilepsy? ☐Yes ☐No

Do you need further explanation of TMS and its associated risks? ☐Yes ☐No

If you answered yes to any of the above, please provide details (use reverse if necessary):

Appendix F: Self-report questionnaires

Appendix F.1 Eating disorder examination questionnaire (EDE-Q) version 6

EDE-Q

The following questions are concerned with the past four weeks only (28 days). Please read each question carefully and tick the appropriate box.

Please answer all the questions.

a. What is your current weight? _____

b. What is the lowest you have ever weighed as an adult (or teenager) since your eating disorder began?

c. What was your height at this time? _____

On how many days out of the past 28 days...	No days	1-5 days	6-12 days	13-15 days	16-22 days	23-27 days	Every day
1. Have you been deliberately trying to limit the amount of food you eat to influence your shape or weight?	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>	5 <input type="checkbox"/>	6 <input type="checkbox"/>
2. Have you gone for long periods of time (8 hours or more) without eating anything in order to influence your shape or weight?	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>	5 <input type="checkbox"/>	6 <input type="checkbox"/>
3. Have you tried to avoid eating foods which you like in order to influence your shape or weight?	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>	5 <input type="checkbox"/>	6 <input type="checkbox"/>
4. Have you tried to follow definite rules regarding your eating in order to influence your shape or weight; for example, a calorie limit, a set amount of food, or rules about what or when you should eat?	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>	5 <input type="checkbox"/>	6 <input type="checkbox"/>
5. Have you wanted your stomach to be empty?	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>	5 <input type="checkbox"/>	6 <input type="checkbox"/>
6. Has thinking about food or its calorie content made it much more difficult to concentrate on things you're interested in;	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>	5 <input type="checkbox"/>	6 <input type="checkbox"/>

for example, read, watch TV or follow a conversation?

7.	Have you been afraid of losing control over eating?	0 <input type="text"/>	1 <input type="text"/>	2 <input type="text"/>	3 <input type="text"/>	4 <input type="text"/>	5 <input type="text"/>	6 <input type="text"/>
8.	Have you had episodes of binge eating?	0 <input type="text"/>	1 <input type="text"/>	2 <input type="text"/>	3 <input type="text"/>	4 <input type="text"/>	5 <input type="text"/>	6 <input type="text"/>
9.	Have you eaten in secret? (Do not count binges)	0 <input type="text"/>	1 <input type="text"/>	2 <input type="text"/>	3 <input type="text"/>	4 <input type="text"/>	5 <input type="text"/>	6 <input type="text"/>

On how many days out of the past 28 days...

No days	1-5 days	6-12 days	13-15 days	16-22 days	23-27 days	Every day
0 <input type="text"/>	1 <input type="text"/>	2 <input type="text"/>	3 <input type="text"/>	4 <input type="text"/>	5 <input type="text"/>	6 <input type="text"/>
0 <input type="text"/>	1 <input type="text"/>	2 <input type="text"/>	3 <input type="text"/>	4 <input type="text"/>	5 <input type="text"/>	6 <input type="text"/>
0 <input type="text"/>	1 <input type="text"/>	2 <input type="text"/>	3 <input type="text"/>	4 <input type="text"/>	5 <input type="text"/>	6 <input type="text"/>
0 <input type="text"/>	1 <input type="text"/>	2 <input type="text"/>	3 <input type="text"/>	4 <input type="text"/>	5 <input type="text"/>	6 <input type="text"/>
0 <input type="text"/>	1 <input type="text"/>	2 <input type="text"/>	3 <input type="text"/>	4 <input type="text"/>	5 <input type="text"/>	6 <input type="text"/>

10.	Have you definitely wanted your stomach to be flat?	0 <input type="text"/>	1 <input type="text"/>	2 <input type="text"/>	3 <input type="text"/>	4 <input type="text"/>	5 <input type="text"/>	6 <input type="text"/>
11.	Has thinking about shape or weight made it more difficult to concentrate on things you are interested in; e.g., read, watch TV or follow a conversation?	0 <input type="text"/>	1 <input type="text"/>	2 <input type="text"/>	3 <input type="text"/>	4 <input type="text"/>	5 <input type="text"/>	6 <input type="text"/>
12.	Have you had a definite fear that you might gain weight or become fat?	0 <input type="text"/>	1 <input type="text"/>	2 <input type="text"/>	3 <input type="text"/>	4 <input type="text"/>	5 <input type="text"/>	6 <input type="text"/>
13.	Have you felt fat?	0 <input type="text"/>	1 <input type="text"/>	2 <input type="text"/>	3 <input type="text"/>	4 <input type="text"/>	5 <input type="text"/>	6 <input type="text"/>
14.	Have you had a strong desire to lose weight?	0 <input type="text"/>	1 <input type="text"/>	2 <input type="text"/>	3 <input type="text"/>	4 <input type="text"/>	5 <input type="text"/>	6 <input type="text"/>

Over the past 4 weeks (28 days)

None of the times	A few of the times	Less than $\frac{1}{4}$ the time	Half the time	More than $\frac{1}{4}$ the time	Most of the time	Every time
0 <input type="text"/>	1 <input type="text"/>	2 <input type="text"/>	3 <input type="text"/>	4 <input type="text"/>	5 <input type="text"/>	6 <input type="text"/>

15.	On what proportion of times that you have eaten have you <u>felt guilty</u> because of the effect on your shape or weight? (Do not count binges)	0 <input type="text"/>	1 <input type="text"/>	2 <input type="text"/>	3 <input type="text"/>	4 <input type="text"/>	5 <input type="text"/>	6 <input type="text"/>
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16. Have there been any times when you have felt that you have eaten what other people would regard as an unusually large amount of food given the circumstances?
- ☐ 0 No ☐ 1 Yes
17. How many such episodes have you had over the past four weeks?
-
18. During how many of these episodes of overeating did you have a sense of having lost control over your eating?
-
19. Have you had other episodes of eating in which you have had a sense of having lost control and eaten too much, but have not eaten an unusually large amount of food given the circumstances?
- ☐ 0 No ☐ 1 Yes
20. How many such episodes have you had over the past four weeks?
-
21. Have you made yourself sick (vomit) as a means of controlling your shape or weight?
- ☐ 0 No ☐ 1 Yes
22. How many times have you done this over the past four weeks?
-
23. Have you taken laxatives as a means of controlling your shape or weight?
- ☐ 0 No ☐ 1 Yes
24. How many times have you done this over the past four weeks?
-
25. Have you taken diuretics (water tablets) as a means of controlling your shape or weight?
- ☐ 0 No ☐ 1 Yes
26. How many times have you done this over the past four weeks?
-

27. Have you exercised hard as a means of controlling your shape or weight?

☐ 0
No

☐ 1
Yes

28. How many times have you done this over the past four weeks?

Over the past 4 weeks (28 days)		Not at all		Slightly		Moderately		Markedly
		0	1	2	3	4	5	6
29.	Has your weight influenced how you think about (judge) yourself as a person?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
30.	Has your shape influenced how you think about (judge) yourself as a person?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
31.	How much would it upset you if you had to weigh yourself once a week for the next four weeks?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
32.	How dissatisfied have you felt about your weight?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
33.	How dissatisfied have you felt about your shape?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
34.	How concerned have you been about other people seeing you eat?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
35.	How uncomfortable have you felt seeing your body; for example, in shop window reflections, while undressing or taking a bath or shower?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
36.	How uncomfortable have you felt about others seeing your body; for example, in communal changing rooms, when swimming or wearing tight clothes?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Appendix F.2 Depression, anxiety and stress scale (DASS-21)

<h1 style="margin: 0;">DASS₂₁</h1>		Name:	Date:
<p>Please read each statement and circle a number 0, 1, 2 or 3, which indicates how much the statement applied to you <i>over the past week</i>. There are no right or wrong answers. Do not spend too much time on any statement.</p> <p><i>The rating scale is as follows:</i></p> <p>0. Did not apply to me at all</p> <p>1. Applied to me to some degree, or some of the time</p> <p>2. Applied to me to a considerable degree, or a good part of time</p> <p>3. Applied to me very much, or most of the time</p>			
1	I found it hard to wind down	0	1 2 3
2	I was aware of dryness of my mouth	0	1 2 3
3	I couldn't seem to experience any positive feeling at all	0	1 2 3
4	I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1 2 3
5	I found it difficult to work up the initiative to do things	0	1 2 3
6	I tended to over-react to situations	0	1 2 3
7	I experienced trembling (eg, in the hands)	0	1 2 3
8	I felt that I was using a lot of nervous energy	0	1 2 3
9	I was worried about situations in which I might panic and make a fool of myself	0	1 2 3
10	I felt that I had nothing to look forward to	0	1 2 3
11	I found myself getting agitated	0	1 2 3
12	I found it difficult to relax	0	1 2 3
13	I felt down-hearted and blue	0	1 2 3
14	I was intolerant of anything that kept me from getting on with what I was doing	0	1 2 3
15	I felt I was close to panic	0	1 2 3
16	I was unable to become enthusiastic about anything	0	1 2 3
17	I felt I wasn't worth much as a person	0	1 2 3
18	I felt that I was rather touchy	0	1 2 3
19	I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)	0	1 2 3
20	I felt scared without any good reason	0	1 2 3
21	I felt that life was meaningless	0	1 2 3

Appendix G: Visual analogue scales (VAS)

Appendix G.1 The 'initial' VAS collected throughout the randomised control trial and within each session of the therapeutic case series

1. Please mark the following line at the point that most accurately reflects your current level of **stress**

Not stressed
at all

Extremely
stressed

2. Please mark the following line at the point that most accurately reflects your current **urge to restrict**

No urge to
restrict at all

Extremely strong
urge to restrict

3. Please mark the following line at the point that most accurately reflects your current **level of anxiety**

Not anxious
at all

Extremely anxious

4. Please mark the following line at the point that most accurately reflects your current **urge to exercise**

No urge to
exercise at all

Extremely strong
urge to exercise

5. Please mark the following line at the point that most accurately reflects the extent to which **you feel full**

Not feeling
full at all

Feeling extremely
full

6. Please mark the following line at the point that most accurately reflects the extent to which **you feel fat**

Not feeling
fat at all

Feeling extremely
fat

Appendix G.2 The ‘additional’ VAS collected during FCT immediately pre and post rTMS in the randomised control trial

7. Please mark the following line at the point that most accurately reflects your current state of **calmness or tension**

Extremely Calm _____ Extremely tense

8. Please mark the following line at the point that most accurately reflects your current **mood**

Extremely low _____ Extremely high

9. Please mark the following line at the point that most accurately reflects your **hunger**

Not hungry at all _____ Extremely hungry

10. Please mark the following line at the point that most accurately reflects your current **urge to eat** (any food of your choice)

No urge to eat at all _____ Extremely strong urge to eat

11. Please mark the following line at the point that most accurately reflects your current **urge to binge eat on any (or all) of these foods.**

No urge to binge eat at all _____ Extremely strong urge to binge eat

12. Please mark the following line at the point that most accurately reflects your current **urge to be sick or purge.**

No urge to be sick or purge _____ Extremely strong urge to be sick or purge

Appendix G.3 The 'food related' VAS collected during the FCT immediately pre and post rTMS in the randomised control trial

Please mark the following lines at the points that most accurately reflect the way that you find the chocolate in front of you

Appearance:

Not appetising
at all

Extremely
appetising

Smell:

Not appetising
at all

Extremely
appetising

Taste:

Not tasty
at all

Extremely
tasty

Urge to eat:

Would not
wish to eat
them at all

Would like to
eat some
very much indeed

Please mark the following lines at the points that most accurately reflect the way that you find the nuts in front of you

Appearance:

Not appetising
at all

Extremely
appetising

Smell:

Not appetising
at all

Extremely
appetising

Taste:

Not tasty
at all

Extremely
tasty

Urge to eat:

Would not
wish to eat
them at all

Would like to
eat some
very much indeed

Please mark the following lines at the points that most accurately reflect the way that you find the biscuits in front of you

Appearance:

Not appetising
at all

Extremely
appetising

Smell:

Not appetising
at all

Extremely
appetising

Taste:

Not tasty
at all

Extremely
tasty

Urge to eat:

Would not
wish to eat
them at all

Would like to
eat some
very much indeed

Please mark the following lines at the points that most accurately reflect the way that you find the crisps in front of you

Appearance:

Not appetising
at all

Extremely
appetising

Smell:

Not appetising
at all

Extremely
appetising

Taste:

Not tasty
at all

Extremely
tasty

Urge to eat:

Would not
wish to eat
them at all

Would like to
eat some
very much indeed

Appendix H: Tasks and measures

Appendix H.1 Instructions and screen shots of the food challenge task (FCT)

Instructions:

You will now be presented with two short video clips of people eating a variety of foods including crisps, chocolate, biscuits and nuts. These same foods will also be present in the room. After viewing the video and looking at the foods presented in front of you, please rate each food according to their appearance, smell, taste and your current urge to eat them.

Screen shots of the food cue video:



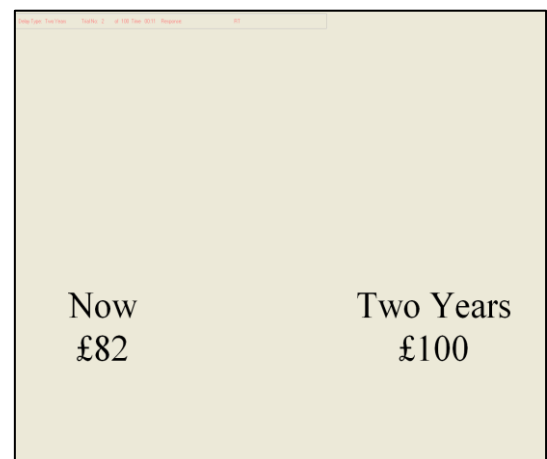
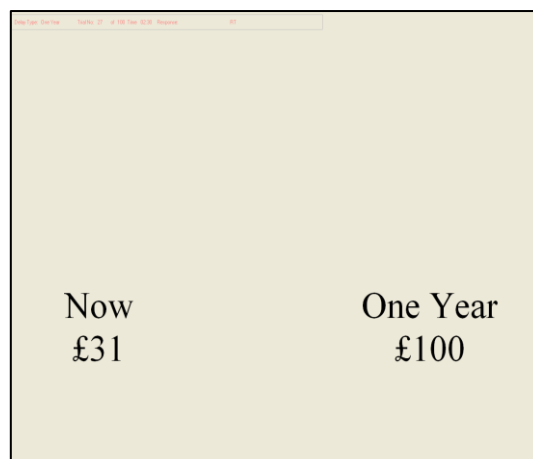


Appendix H.2 Instructions and screen shots of the temporal discounting (TD) task

Instructions:

You will now be asked to complete a short, computerised task which requires you to choose between a hypothetical, smaller amount of money immediately or a larger amount of money at a later date. Please try to make a decision which would most accurately reflect how you would behave if you were presented with such a choice in reality. Please press the left mouse button to choose the immediate value of money offered, and the right mouse button to choose the amount offered in the future. If you have any questions at this point please don't hesitate to ask one of the researchers.

Screen shots of the computerised temporal discounting task:



Appendix H.3 Instructions for the collection of saliva samples

Saliva as a sample material

With the rising diagnostic importance of analytes with rhythmically changing value (e.g. hormones or drugs) it is necessary to easily obtain high quality diagnostic samples.

Several research studies have determined that saliva is effective and useful as a sample material.

The Salivette® provides an optimal method for hygienic collection of saliva. Patients can very easily and independently collect the sample material for daily profiles at home without professional medical assistance.

For saliva collection, the Salivette® is available with different swab options: a plain cotton swab, a cotton swab with citric acid preparation to stimulate salivation, and a synthetic swab specially designed for cortisol determination.

Salivette® – Instructions for use



1 The patient removes the swab from the Salivette® (see Figs. 1 and 2)...



3 ...and places the swab in the mouth and chews it for about 45 seconds to stimulate salivation (see Fig. 3).



4 Now the patient returns the swab with the absorbed saliva to the Salivette® (see Fig. 4)...



5 ...and replaces the stopper (see Fig. 5).



6 Centrifugation for 2 minutes at 1,000 x g yields a clear saliva sample in the conical tube (see Fig. 6).



7 Particles and mucus strands are collected in the specially designed extended tip of the Salivette® tube (see Fig. 7).



8 The closed insert containing the swab is then hygienically disposed. The saliva recovered can now be used for analysis (see Fig. 8).

Appendix I: Other information

Appendix I.1 Standard explanations of TMS given to participants in the RCT

This is the device that generates the localised magnetic waves that are used to stimulate the brain. In this coil, there is an electric current that generates a magnetic field. It is important for you to know that you will not be in contact with the electric current as it runs inside the coil. To deliver the magnetic waves to the brain, this coil will be held against your head. TMS is a safe technique however, some people have found receiving rTMS to be a bit uncomfortable. It is important for you to know that the effects vary markedly between individuals and that both people who received sham (a placebo) or real rTMS have reported a range of experiences. These experiences range from 'feeling nothing at all' to a strong 'tapping' or 'woodpecker' sensation. Most of the people who reported these effects stated that it got less uncomfortable during the duration of the session.

There are two part to the stimulation section of the study: 1) stimulating your motor cortex and 2) delivery of the rTMS. Firstly, in order to know where to hold the coil in relation to your brain in particular we need to register the image gained from the MRI scan you had previously, to where you are seated currently. This is somewhat like how a satnav works – we need to tell the computer where you and the coil are so that it can relate this information to the picture of your brain we gained from the MRI scan. You will be required to wear a headband in order to do this, please try not to move this headband once it is in place.

1) Motor cortex: In the first section we will locate a part of the brain that is called the motor cortex. We are aiming to find the spot on the left side of your skull that, if we stimulate it, will activate the muscles in your right hand. When we are looking for this area you will hear a clicking sound from time to time. Every click represents a single stimulation pulse with magnetic waves. The reason we need to do this is because the 'excitability' of people's brain differs between individuals. This allows us to find the lowest possible intensity on an individual basis with which we can stimulate your brain in the second part of

the session. Sometimes this process can take a little time which is completely normal.

2) rTMS session: After stimulating the motor cortex, we will begin the rTMS session to the left frontal part of the brain. You will now hear the same clicking sound but in shorter more rapid bursts. These are what we call 'trains' of stimulation – they last for 5 seconds and there is a 55 second break in between each train. You will receive 20 trains like this, therefore this part of the session will last for approximately 20 minutes. We will always let you know when the next train is about to start by counting down from 5 seconds. Please do not close your eyes during the delivery of the stimulation.

Halfway through the stimulation session we will take your blood pressure and pulse. There is, in our experience, no evidence that rTMS affects blood pressure or pulse changes. This is just an additional safety measure. One thing that may happen during the stimulation session is that the coil may warm up. This is never to a degree that it would hurt you, but there is an inbuilt safety mechanism in the machine that stops it from working when it gets hot. If that were to happen, we will need to change the coils. When we do this it is important for you to know that the condition (real or sham rTMS) will not be changed - the coil will just be replaced by a similar coil.

Appendix I.2 Personal instructions for Brainsight® neuronavigation set-up

1. Find scans from dougal, put all in basket, use cyberduck (**/data/blinded/CNSCNSA**) to download onto desktop
2. Select anatomical data set (participants MRI)
 - Click file chooser (green)
 - Accepts NIfTI, DICOM, PAR?REC, Analyse files
 - Mini brain scan image will appear, select one file
3. Co-register with Talairach space:
 - Chose new, manual AC-PC option
 - Find and mark AC/PC (see diagram) select next step
 - Make bounding box to include edges of brain
 - Make sure AC/PC and callosum lines up, make any adjustments then click finish
4. ROIs/Overlays: N/A (overlays for use with fMRI data)
5. Reconstructions:
 - new, skin (include whole head in box, make sure nose is in picture), exit
 - new, curvilinear/brain reconstruction (include just brain in box, in order to see detailed brain anatomy/sulci use peel), exit
6. Anatomical landmarks:
 - Select homologous anatomical landmarks for participants
 - new, nose bridge, set crosshairs
 - new, nose tip, set crosshairs
 - new, right ear, set crosshairs
 - new, left ear, set crosshairs (remember to account for earplugs with ear tragus so put slightly in front)
7. Configure targets:
 - new, name leftDLPFC, use trajectory
 - Enter Talairach co-ordinates:
 - **x = - 45, y = 45, z = 35** (based on Fitzgerald (2009): between centre BA9/border BA46) and name marker leftDLPFC
 - Ensure trajectory marker is lined up correctly too (green cone should line up on red marker), set crosshairs
 - SAVE PROJECT! (so that target is saved, set to cross hairs)