An investigation into the therapeutic utility of transcranial direct current stimulation in bulimia nervosa

Kekic, Maria

Awarding institution:
King's College London

An investigation into the therapeutic utility of transcranial direct current stimulation in bulimia nervosa

---

Maria Kekic

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

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

Doctor of Philosophy (PhD)

2016

ABSTRACT

Background: Recent neurobiological insights gained from functional neuroimaging studies suggest that bulimia nervosa (BN) is underpinned by dysregulated frontostriatal circuitry, which supports self-regulatory control and food reward processing capacities. Brain-directed interventions may therefore hold promise as treatments for the disorder. The overarching aim of this research was to investigate the therapeutic utility of transcranial direct current stimulation (tDCS; a form of non-invasive brain stimulation) in patients with BN.

Methods: Four studies were conducted: (1) a systematic review of the clinical efficacy of tDCS across all psychiatric disorders; (2) a randomised controlled trial (RCT) of single-session tDCS applied to the dorsolateral prefrontal cortex (DLPFC) in healthy individuals with frequent food cravings; (3) a cross-sectional study of temporal discounting (a marker of poor self-regulatory control) in patients with BN and healthy controls; and (4) an RCT of single-session tDCS applied to the DLPFC in BN.

Results: The main findings were as follows: (1) existing data indicate that tDCS interventions comprising multiple sessions can ameliorate symptoms of several major psychiatric disorders, both acutely and in the long-term; (2) a single session of sham-controlled DLPFC tDCS transiently suppressed craving for sweet foods (i.e., altered food reward processing) among individuals with frequent food cravings; (3) patients with BN showed greater temporal discounting (i.e., poorer self-regulatory control) relative to healthy participants; and (4) a single session of sham-controlled DLPFC tDCS temporarily reduced symptoms, improved mood, and lowered temporal discounting (i.e., increased self-regulatory control) in individuals with BN.

Conclusions: Taken together, the results provide preliminary support for the therapeutic utility of tDCS over the DLPFC in BN, and offer justification for multi-session trials in this patient population.

ACKNOWLEDGEMENTS

I would firstly like to say an enormous thank you to my amazing supervisors – Professors Ulrike Schmidt and Iain Campbell. I feel so grateful to have had the opportunity to complete a PhD under the supervision of such a talented, caring, supportive, approachable, easy-going, and fun double-act! You have made this experience so enjoyable, and have each taught me so much along the way. Thank you for everything.

Secondly, I would like to thank the rest of the team at 103 – past and present. I can't believe how many incredible people have ended up working together under one roof. Thank you for making it such a fun and friendly environment to work in, which oozes energy and positivity. I would like to say a special thank you to the girls who have become my very close friends (you know who you are!) – thanks for the endless smiles and laughter. An extra special thank you goes to Jess – I am so appreciative of your extremely special friendship and have no doubt it will last a lifetime.

Thirdly, I want to thank my family and close friends outside of King's ('the Manner girls!'). Thank you for your love and support throughout, and for continually showing an interest in my work. In particular, thank you to my parents and older sister, Natalia, for always being proud of me, and to Shannon – the best friend and roomie anyone could ask for.

Lastly, thank you to Tony David for letting me use his equipment, and to all the unsuspecting participants who put their trust in me to zap their brains! Thank you for the interesting chats in the lab, and for caring enough to get involved in the research – it wouldn't have been possible without you.

LIST OF IMPORTANT ABBREVIATIONS[1]

AN	anorexia nervosa
AL/CR	anode left/cathode right
AR/CL	anode right/cathode left
BED	binge-eating disorder
BMI	body mass index
BN	bulimia nervosa
DASS	Depression Anxiety and Stress Scales
DF	discount factor
DGI	Delaying Gratification Inventory
DLPFC	dorsolateral prefrontal cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
ED	eating disorder
EDDS	Eating Disorder Diagnostic Scale
EDE-Q	Eating Disorder Examination-Questionnaire
FCT	Food Challenge Task
FCQ-(T/S)	Food Craving Questionnaire-(Trait/State)
(f)MRI	(functional) magnetic resonance imaging
HC	healthy control
ICD	International Statistical Classification of Diseases and Related Health Problems
KCL	King's College London
LL	larger-later

[1] As this is a thesis incorporating publications, and the body text of each publication has been left largely unchanged, acronyms are re-introduced in each chapter and some are chapter-specific.

M	mean
MDD	major depressive disorder
MEDCQ-R	Mize's Eating Disorder Cognitions Questionnaire-Revised
NHS	National Health Service (UK)
NIBS	non-invasive brain stimulation
NICE	National Institute for Health and Care Excellence (UK)
NIMH	National Institute of Mental Health (US)
PANAS	Positive and Negative Affect Schedule
POMS	Profile of Mood States
RCT	randomised controlled trial
(r)TMS	(repetitive) transcranial magnetic stimulation
SCID	Structured Clinical Interview for Diagnostic and Statistical Manual Disorders
SD	standard deviation
SE	standard error
SS	smaller-sooner
SUD	substance use disorder
TD	temporal discounting
tDCS	transcranial direct current stimulation
VAS	visual analogue scale

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PAPERS ASSOCIATED WITH THIS THESIS

Kekic, M., Boysen, E., Campbell, I. C., & Schmidt, U. (2016). A systematic review of the clinical efficacy of transcranial direct current stimulation (tDCS) in psychiatric disorders. *Journal of Psychiatric Research, 74,* 70-86. **(Chapter 2).**

Kekic, M., McClelland, J., Campbell, I. C., Nestler, S., Rubia, K., David, A. S., & Schmidt, U. (2014). The effects of prefrontal cortex transcranial direct current stimulation (tDCS) on food craving and temporal discounting in women with frequent food cravings. *Appetite, 78,* 55-62. **(Chapter 3).**

Kekic, M., Bartholdy, S., Cheng, J., McClelland, J., Boysen, E., Musiat, P.,… Schmidt, U. (2016). Increased temporal discounting in bulimia nervosa. *International Journal of Eating Disorders, 49,* 1077-1081. **(Chapter 4).**

Kekic, M., McClelland, J., Bartholdy, S., Boysen, E., Musiat, P., Dalton, B.,… Schmidt, U. (2017). Transcranial direct current stimulation improves symptoms, mood, and self-regulatory control in bulimia nervosa: A randomised controlled trial. *PLOS ONE, 12*(1). **(Chapter 5).**

CONFERENCE AND RESEARCH PRESENTATIONS ASSOCIATED WITH THIS THESIS

Kekic, M., Campbell, I. C. & Schmidt, U. (2016). Transcranial direct current stimulation improves symptoms, mood, and self-regulatory control in bulimia nervosa: a proof-of-principle clinical trial. Poster presentation at the European College of Neuropsychopharmacology Congress in Vienna, Austria.

Kekic, M., Campbell, I. C. & Schmidt, U. (2016). Transcranial direct current stimulation improves symptoms and cognitive control in bulimia nervosa: A proof-of-principle clinical trial. Oral presentation at the Academy for Eating Disorders (AED) International Conference on Eating Disorders (ICED) in San Francisco, US.

Kekic, M., Campbell, I. C. & Schmidt, U. (2016). Bad things come to those who don't wait: Temporal discounting is associated with compulsive overeating, eating disorder psychopathology, food addiction, and high BMI. Oral presentation at the AED ICED in San Francisco, US.

Kekic, M., Campbell, I. C. & Schmidt, U. (2015). The effects of prefrontal cortex transcranial direct current stimulation (tDCS) on food craving and impulsivity in women with frequent food cravings. Oral presentation at the AED ICED in Boston, US.

Kekic, M., Campbell, I. C. & Schmidt, U. (2015). Transcranial direct current stimulation: a promising novel treatment for bulimia nervosa. Poster presentation at the National Institute of Health Research Biomedical Research Centre and Dementia Unit Retreat in London, UK.

The research reported in this thesis has also been presented at departmental meetings and student showcase events at the Institute of Psychiatry, Psychology & Neuroscience, King's College London.

DECLARATION OF CANDIDATE'S ROLE

Chapter 1: General introduction

All work is the candidate's own.

Chapter 2: A systematic review of the clinical efficacy of transcranial direct current stimulation in psychiatric disorders

The candidate was the main contributor to the development and execution of this systematic review. The literature search and quality assessment were conducted independently by the candidate and by an undergraduate student completing a placement at King's College London (KCL) – Miss Elena Boysen. The paper which forms this chapter was written by the candidate, with limited input from the co-authors listed on the publication.

Chapter 3: The effects of prefrontal cortex transcranial direct current stimulation on food craving and temporal discounting in women with frequent food cravings

The application for ethical approval, recruitment of participants, and the collection, entry, and analysis of data were carried out by the candidate during her MSc degree; however, the paper which forms this chapter was written and published by the candidate during this PhD. Limited input was provided from the co-authors of the publication.

Chapter 4: Increased temporal discounting in bulimia nervosa

This study used data from two distinct experiments: one was led by the candidate (discussed in chapter 5; see below) and the other by another PhD student at KCL – Miss Savani Bartholdy. Data were combined and analysed by the candidate, and the paper which forms this chapter was written jointly by the candidate and Miss Savani Bartholdy, with limited input from the other co-authors listed on the publication.

Chapter 5: Transcranial direct current stimulation improves symptoms, mood, and self-regulatory control in bulimia nervosa: A randomised controlled trial

The application for ethical approval, recruitment of participants, and the collection, entry, and analysis of data were performed by the candidate. Due to the design of the trial, the tDCS technician (the candidate) could not be blinded; therefore, an additional investigator was needed during each study session to administer the experimental measures. This role was primarily undertaken by Miss Elena Boysen, Miss Savani Bartholdy, or Dr Jessica McClelland (a postdoctoral researcher at KCL). The paper which forms this chapter was written by the candidate, with limited input from the co-authors.

Chapter 6: General discussion

All work is the candidate's own.

Chapter 1. General introduction

Advancing the understanding and treatment of eating disorders (EDs), including bulimia nervosa (BN), is an issue of immense public health importance and is recognised as an area of high priority by the US National Institute of Mental Health (NIMH) (Chavez & Insel, 2007). In recent years these psychiatric disorders, which were long thought to stem from purely psychological processes, have gained increasing recognition as physiological disorders of the brain (Chavez & Insel, 2007; Insel, 2010; Schmidt & Campbell, 2013; van Elburg & Treasure, 2013). One implication of this recognition is that the treatment of BN and other EDs can be approached with methods of modern neuroscience (Chavez & Insel, 2007). Indeed, the NIMH's Research Domain Criteria project endorses the harnessing of neuroscience tools, such as neuromodulation, in the service of more effective therapeutic strategies (Cuthbert, 2014).

This introductory chapter first describes the history, diagnostic criteria, epidemiology, course and outcome, pathogenesis, and treatment of BN. Following this, the neurobiology of the disorder is examined, including a brain-based developmental model of illness. Lastly, an overview of transcranial direct current stimulation (tDCS) – a neuromodulatory technique with potential clinical applications in neuropsychiatry – is presented.

1.1 BULIMIA NERVOSA: AN OVERVIEW

The Oxford English Dictionary defines BN as "an [ED] characterised by regular, usually secretive bouts of binge-eating followed by self-induced vomiting, purging, strict dieting, or extreme exercise, in association with persistent over-concern with body weight" (2016).

1.1.1 History

Scattered historical references to ancient practices of binge-eating and purging suggest that BN has existed since the Middle Ages; however, the ED was first named and described clinically as an "ominous variant of anorexia nervosa" (AN)[2] in 1979 by the British professor and psychiatrist, Gerald Russell[3] (Russell, 1979). Russell (1979) reported on a series of 30 patients whose illness resembled AN, but who did not necessarily reduce their food intake: these individuals were said to engage in frequent episodes of overeating, immediately followed by habitual self-induced vomiting and/or purging in an attempt to counteract the increased calorie intake. Based on prospective observations of this patient group over a six-and-a-half-year period, Russell (1979) specified a set of clear diagnostic criteria to enable other clinicians and researchers to identify the proposed condition:

> (1) the patients suffer from powerful and intractable urges to overeat;
>
> (2) they seek to avoid the 'fattening' effects of food by inducing vomiting or abusing purgatives or both;
>
> (3) they have a morbid fear of becoming fat.

One year after Russell's clinical description of BN was published, the disorder was formally recognised by the international scientific world for the first time. Initially, 'bulimia' was defined in the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (*DSM-III*) (American Psychiatric Association, 1980) as a disorder that required the presence of binge-eating and little else (Palmer, 2004); however, this was

[2] AN is an ED characterised by extremely low bodyweight and an irrational fear of weight gain (see section 1.1.2.2).

[3] The term 'bulimia nervosa' was suggested by Dr Patrick Campbell.

later replaced by BN in the *DSM-III, Revised* (American Psychiatric Association, 1987), with diagnostic criteria more closely resembling those proposed by Russell. In 1992, a similar entry was included in the first volume of the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (*ICD-10*) (World Health Organisation, 1992).

1.1.2 Current diagnostic criteria

Although there is an ongoing debate concerning the validity and usefulness of diagnosis in psychiatry (see section 6.6.6; Timimi, 2013), most clinicians and researchers regard categorical classification as having some value (Tyrer, 2014). This is because it facilitates effective communication of information relating to the clinical characteristics, pathogenesis, prognosis, and indicated treatment options associated with a disorder (Casey et al., 2013; Mellsop, Menkes, & El-Badri, 2007; Tyrer, 2014). At present, there are two widely established systems for classifying mental disorders, including BN: the 'Mental and Behavioural Disorders' chapter of the *ICD* (currently in its 10th revision with a 2016 electronic update; World Health Organisation, 2016) and the *DSM* (currently in its 5th edition; American Psychiatric Association, 2013). While there is substantial convergence between the two classification systems, the *DSM* is generally considered more 'accurate' than the *ICD*, partly due to its use of operational criteria (Tyrer, 2014), and therefore tends to be the favoured diagnostic tool in research settings (Mezzich, 2002). Current diagnostic criteria for BN as well as for the other EDs are provided below.

1.1.2.1 Bulimia nervosa

The *ICD-10* (World Health Organisation, 2016) classifies BN as an ED "characterised by repeated bouts of overeating and an excessive preoccupation with the control of body

weight, leading to a pattern of overeating followed by vomiting or use of purgatives". The disorder is also acknowledged as sharing "many psychological features with AN, including an over-concern with body shape and weight". Disorders that fulfil some but not all of the features of BN may be categorised as atypical BN.

BN is listed in the 'Feeding and Eating Disorders' chapter of the *DSM, Fifth Edition* (*DSM-5*) (American Psychiatric Association, 2013). According to the manual, there are three essential features of the condition:

> (1) recurrent episodes of binge-eating (eating, in a discrete period of time, an amount of food that is larger than most individuals would eat in a similar period of time under similar circumstances, accompanied by a sense of lack of control);
>
> (2) recurrent inappropriate compensatory behaviours to prevent weight gain (e.g., self-induced vomiting, misuse of laxatives/diuretics, fasting, or excessive exercise);
>
> (3) self-evaluation that is unduly influenced by body shape and weight.

To qualify for the diagnosis, the binge-eating and inappropriate compensatory behaviours must both occur, on average, at least once a week for three months. Individuals who meet the criteria for BN but whose symptoms are of low frequency and/or limited duration may be diagnosed with a form of 'other specified feeding or eating disorder' (OSFED). It should be noted that the symptom frequency requirement for BN was reduced in the *DSM-5* from a more stringent twice weekly in the *DSM, Fourth Edition* (*DSM-IV*; American Psychiatric Association, 2000) in an attempt to reduce the number of patients falling into this residual category (known previously as 'eating disorder not otherwise specified' [EDNOS]). Individuals with BN are typically within the normal weight or overweight range (body mass index [BMI] ≥ 18.5 and < 30 in adults).

1.1.2.2 Other eating disorders

Along with BN, a number of additional EDs are defined in the *ICD-10* (World Health Organisation, 2016) and *DSM-5* (American Psychiatric Association, 2013). Whilst a discussion of all of these is beyond the scope of this thesis, it is important to consider BN in the context of the other major EDs: AN and binge-eating disorder (BED). For brevity, and because BED is not currently included in the *ICD-10* (World Health Organisation, 2016), only *DSM-5* (American Psychiatric Association, 2013) diagnostic criteria are presented here.

An individual will receive a *DSM-5* (American Psychiatric Association, 2013) diagnosis of AN if they:

(1) restrict their energy intake relative to requirements, leading to a significantly low body weight that is less than minimally normal or expected (BMI < 18.5 in adults);

(2) have an intense fear of gaining weight/becoming fat, or engage in persistent behaviour that interferes with weight gain;

(3) display disturbances in the way their body weight/shape are experienced, assign undue influence of body weight/shape on their self-evaluation, or have a persistent lack of recognition of the seriousness of their current low body weight.

Two subtypes of the disorder are described in the manual: restricting type, in which the patient does not engage in recurrent episodes of binge-eating or purging behaviour, and binge-eating/purging type, in which they do.

BED was officially recognised as a distinct ED diagnosis for the first time in the *DSM-5* (American Psychiatric Association, 2013). The essential feature of this condition is recurrent episodes of binge-eating (defined in section 1.1.2.1) that must occur, on average, at least once per week for three months. In contrast to that in BN, binge-eating in BED is not accompanied by extreme efforts to counteract it and, as such, individuals with the disorder are often overweight or obese (BMI $\geq$ 25 in adults).

1.1.3 Epidemiology

Epidemiology is the study of how often illnesses occur in different groups of people. Information gained from epidemiological studies is used to guide the development of intervention and prevention strategies; however, such investigations present multiple challenges in the field of EDs. For example, population base rates are low, which necessitates large samples in order to detect cases (Mitchison & Mond, 2015), and this problem is compounded by the tendency for individuals with EDs (males, in particular) to conceal their condition and avoid professional help (Hoek & van Hoeken, 2003). A further difficulty relates to the extensive use of *DSM-IV* classification criteria, which has resulted in an over-representation of the EDNOS diagnostic category (Mitchison & Mond, 2015) and an under-representation of people with BN (see section 1.1.2.1). Nevertheless, available data on the epidemiology of BN are summarised below.

1.1.3.1 Incidence

Incidence rate refers to the number of new cases of a disorder in a defined population over a specified period of time (usually one year). Limited incidence studies of BN have been conducted; however, in a review of those that have, Smink, van Hoeken, and Hoek (2012) reported overall primary-care incidence rates (per 100,000 persons per year) ranging from 6.1 in the Netherlands from 1995-1999 to 12.2 in the UK in 1993. In

community studies considering the group at highest risk (i.e., young females), and diagnoses in accordance with *DSM-5* criteria, rates of up to 300 per 100,000 persons per year have been documented (Smink, van Hoeken, & Hoek, 2013). By contrast, incidence rates for males have been calculated at just 0.7-0.8 per 100,000 persons per year (Currin, Schmidt, Treasure, & Jick, 2005; Hoek & van Hoeken, 2003).

Data concerning time trends in the incidence of BN are somewhat inconsistent; for example, a Danish nationwide psychiatric registry study found that rates increased from 6.3 to 7.2 per 100,000 persons per year between 1995 and 2010 (Steinhausen & Jensen, 2015), whilst the overall incidence rate of BN in Dutch primary-care has reportedly decreased significantly over the past three decades (Smink et al., 2016). In the UK, a threefold increase in the primary-care incidence of BN in 10-39-year-old women was observed between 1988 and 1993 (Turnbull, Ward, Treasure, Jick, & Derby, 1996), followed by a decrease between 1996 and 2000 (Currin et al., 2005), and a period of stability among males and females aged 10-49 during the first decade of the 2000s (Micali, Hagberg, Petersen, & Treasure, 2013).

1.1.3.2 Prevalence

Prevalence refers to the proportion of a population that has a disorder at a specific point or interval in time: at a certain date (point prevalence), in a certain year (one-year prevalence), or at any point in a life (lifetime prevalence). Prior to the reduction of the required minimum frequency of binge-eating and inappropriate compensatory behaviours in the *DSM-5*, the generally accepted prevalence rate for BN was approximately 1% among young females in Western countries (Hoek & van Hoeken, 2003; Smink et al., 2012). Lifetime prevalence estimates for this group have since been calculated at 2.6% for full-syndrome BN and 4.4% for subthreshold BN (Stice, Marti, &

Rohde, 2013). Hudson, Hiripi, Pope, and Kessler (2007) reported a lifetime prevalence of 0.5% for *DSM-IV* BN among males in the US; however, comparable data in accordance with *DSM-5* diagnostic criteria are currently unavailable.

Studies investigating time trends have shown that the point prevalence of BN among university students in the US decreased from 4.2% in 1982 to 1.3% in 1992, but remained relatively stable from the 1990s to the early 2000s (Crowther, Armey, Luce, Dalton, & Leahey, 2008; Keel, Heatherton, Dorer, Joiner, & Zalta, 2006).

1.1.3.3 Gender ratio

Women are more affected by BN than men. Estimates of the female-male ratio are highly variable, ranging from 3:1 (Woodside et al., 2001) to 15:1 (Micali et al., 2013) and 20:1 (Steinhausen & Jensen, 2015).

1.1.4 Course and outcome

Course refers to the temporal pattern of an illness from onset to subsequent recovery, partial recovery, non-recovery, or death, while outcome describes the state of affected individuals at some specified time after the development of a disorder (Sullivan, 2005). ED course and outcome data can be used to inform patients and their families about prognosis, to help clinicians plan and balance their caseloads, and to aid our understanding of the classification of these conditions (Keel & Brown, 2010). However, as with epidemiological studies in EDs, those investigating course and outcome are associated with a number of complexities. For example, the field lacks unified definitions of stage of illness, remission, recovery, and relapse, and the resultant lack of consistency makes comparisons across studies very difficult (Berkman, Lohr, & Bulik, 2007). A problem also exists in the heterogeneity of the diagnostic criteria used to

identify BN samples (Quadflieg & Fichter, 2003), which is primarily due to the major developments that have occurred in various editions of the *DSM* (see section 1.1.2.1). The following data should therefore be considered in this context.

1.1.4.1 Age at onset

BN usually begins in late adolescence or early adulthood. A recent study of 427 outpatients with BN in Italy found that the group had a mean age at onset of 18.2 years (Volpe et al., 2016). This is consistent with previous research indicating that the median age at onset in a nationally representative US sample was 18.0 years (Hudson et al., 2007), and that the peak age of incidence of BN among Finnish women was 16-20 years (Keski-Rahkonen et al., 2009). There is evidence to suggest that the age at onset of BN has decreased over the past three decades (Favaro, Caregaro, Tenconi, Bosello, & Santonastaso, 2009; van Son, van Hoeken, Bartelds, van Furth, & Hoek, 2006), although this may simply be a consequence of increased awareness of BN and thus earlier detection and diagnosis.

1.1.4.2 Remission, recovery and relapse

Keel and Brown (2010) reviewed studies describing ED course and outcome and found that remission rates in patients with BN increased with longer duration of follow-up – from 27% at 1-year follow-up (Bailer et al., 2004a) to 75% at 20-year follow-up (Keel, Gravener, Joiner, & Haedt, 2010), though most individuals achieved remission by 5 years following intake. In their review of 79 studies covering data from 5,653 individuals suffering from BN, Steinhausen and Weber (2009) found that, on average, 45% of the patients showed a full recovery, 27% improved considerably, and 23% had a chronic and protracted course of illness.

Estimates of relapse for BN vary considerably (from 17 to 63%) depending on the definition of relapse and the length of follow-up, with the first six months following remission constituting a peak period for the return of binge/purge symptoms (Olmsted, MacDonald, McFarlane, Trottier, & Colton, 2015; Quadflieg & Fichter, 2003). Many individuals who recover from BN have residual features of the disorder such as over concern about shape and weight, a tendency to restrict dietary intake, and low self-esteem (Sullivan, 2005). This enduring psychopathology is one of the most commonly identified predictors of relapse in BN (Fairburn, Peveler, Jones, Hope, & Doll, 1993; Halmi, Agras, Mitchell, & et al., 2002; Keel, Dorer, Franko, Jackson, & Herzog, 2005).

1.1.4.3 Psychiatric comorbidity

Psychiatric comorbidity is the rule rather than the exception for patients with BN (Treasure, Claudino, & Zucker, 2010). The results of a large-scale nationally representative interview survey in the US showed that 88.0% of adolescents with BN and 94.5% of adults with BN met the criteria for at least 1 comorbid mental disorder (Hudson et al., 2007; Swanson, Crow, Le Grange, Swendsen, & Merikangas, 2011). Furthermore, BN was significantly associated with almost all of the core *DSM-IV* mood, anxiety, impulse-control, and substance use disorders (Hudson et al., 2007; Swanson et al., 2011). In an earlier review of ED comorbidity research, O'Brien and Vincent (2003) identified major depression as the most commonly diagnosed comorbid disorder in individuals with BN, while rates of obsessive-compulsive disorder, substance abuse, and borderline personality disorder were also consistently elevated.

1.1.4.4 Physiological morbidity

BN is associated with a number of serious medical complications. Most notably, fluid and electrolyte disturbances occur in approximately 50% of patients as a result of

excessive vomiting and/or laxative and diuretic misuse, and these can be life-threatening (Crow & Eckert, 2016; Westmoreland, Krantz, & Mehler, 2016). In addition, people with BN often have intermittent amenorrhea, enlarged salivary glands, and dental problems relating to the erosion of tooth enamel (Crow & Eckert, 2016).

1.1.4.5 Mortality

Data show that individuals with BN have an increased risk of both all-cause and suicide mortality; for example, Crow et al. (2009) conducted a longitudinal assessment of 906 individuals with BN and found that 3.9% of the sample had died after the 8-25-year follow-up period (23% of these deaths were attributable to suicide). A similar result was obtained by Franko et al. (2013), who reported that 2 of 60 (3.3%) participants with BN died during a median follow-up period of 20 years, although no suicides were recorded. A recent meta-analysis of mortality rates in BN found them to be modestly elevated: the crude mortality rate (which can be understood in the same way as the incidence rate, when the event being measured is death) was 1.74 per 1000 persons per year (Arcelus, Mitchell, Wales, & Nielsen, 2011).

1.1.5 Pathogenesis

BN is a complex and multifaceted disorder associated with numerous determinants of risk and susceptibility. Factors contributing to disease pathogenesis span three broad categories – biological, psychological, and sociocultural – and can also be considered as predisposing, precipitating, or perpetuating (Watkins, 2011). Several comprehensive reviews have examined the aetiology of BN in detail (Jacobi, Hayward, de Zwaan, Kraemer, & Agras, 2004; Polivy & Herman, 2002; Treasure et al., 2010; Waller & Sheffield, 2008), and a general overview of the current evidence base is provided below.

1.1.5.1 Biological factors

Disordered eating behaviour and associated psychopathology are increasingly conceptualised as biological phenomena. This is predominantly due to a rapidly growing literature substantiating the neurobiological basis of EDs (see section 1.2[4]) and to evidence revealing significant genetic influences[5] on the liability to these conditions. Studies have consistently reported a raised rate of BN among the relatives of individuals who have an ED, suggesting both familial aggregation and a shared transmissible vulnerability to BN (Watkins, 2011); for example, a large controlled family study showed that first-degree female relatives of probands with AN or BN had a fourfold increased risk of developing BN compared with relatives of unaffected controls (Strober, Freeman, Lampert, Diamond, & Kaye, 2000). Twin studies have confirmed that BN is familial whilst distinguishing genetic from environmental contributions, though heritability estimates have varied drastically from 28-83% (Hinney & Volckmar, 2013), and it is unclear from such research whether there is a unique genetic risk for the development of EDs or whether the genetic vulnerability is shared with other psychiatric illnesses (Watkins, 2011).

In addition to family and twin methodologies, modern advances in quantitative and molecular genetics have been applied to the study of EDs. Several candidate gene studies have reported significant associations between BN and polymorphisms in the serotonergic (Ricca et al., 2002), appetite (Miyasaka et al., 2006), oestrogen (Nilsson et al., 2004), and cannabinoid (Monteleone et al., 2009) systems, and variants of the brain-

[4] Due to their relevance and centrality to this thesis, neurobiological factors relating to the pathogenesis of BN are dealt with in detail in a discrete section.

[5] Genetic influences are regarded as distinct to neurobiological mechanisms in this thesis.

derived neurotrophic factor (*BDNF*; Ribases et al., 2004) and alpha-ketoglutarate-dependent dioxygenase (*FTO*; Muller et al., 2012) genes have also been implicated. Nevertheless, contradictory findings are abundant and adequately powered genome-wide association studies must be conducted in order to fully elucidate the genetic architecture of BN (Trace, Baker, Peñas-Lledó, & Bulik, 2013).

1.1.5.2 Psychological factors

Numerous psychological factors have been postulated as specific contributors to the development of BN. These include low self-esteem, body dissatisfaction, and affective disturbances (Polivy & Herman, 2002; Stice, 2002), as well as certain personality traits such as perfectionism (Bulik et al., 2003), obsessive-compulsiveness, impulsivity (Newton, Freeman, & Munro, 1993), sensation-seeking (Rossier, Bolognini, Plancherel, & Halfon, 2000), and narcissism (Steiger, Jabalpurwala, Champagne, & Stotland, 1997), all of which have been shown to predict increases in bulimic symptoms. In addition, various interpersonal experiences – such as childhood sexual abuse, trauma, and teasing – have been associated with the disorder (Hastings & Kern, 1994; Kanakis & Thelen, 1995; Rorty & Yager, 1996).

Many psychological theories have been proposed over the years in an attempt to combine such putative causal factors into a comprehensive whole (Polivy & Herman, 2002). Most influential in terms of treatment have been cognitive behavioural models (Fairburn & Harrison, 2003), which posit that BN develops and is perpetuated as a result of a vicious feedback cycle of interrelated cognitions and behaviours associated with a dysfunctional system for evaluating self-worth, extreme concerns about shape and weight, strict dieting, a perceived lack of self-control, binge-eating, and inappropriate compensatory behaviours (Fairburn, Marcus, & Wilson, 1993). Additional

maintaining mechanisms acknowledged in extensions of the original theories are clinical perfectionism, core low self-esteem, mood intolerance, and interpersonal difficulties (Fairburn, Cooper, & Shafran, 2003).

1.1.5.3 Sociocultural factors

EDs do not occur uniformly in all cultures at all times (Polivy & Herman, 2002). Sociocultural theorists argue that, in Westernised societies, greater exposure and pressure to obtain the 'thin-ideal', internalisation of this thin-ideal, and thinness expectancies increase the risk for BN and other EDs in females (Culbert, Racine, & Klump, 2015). Considerable evidence supports this claim; for example, perceived pressure to be thin has been shown to predict the onset of binge-eating (Stice, Presnell, & Spangler, 2002) and purging behaviours (Field, Camargo, Taylor, Berkey, & Colditz, 1999), and a prospective naturalistic study of Fijian schoolgirls found that bulimic pathology emerged following prolonged exposure to Western television (Becker, Burwell, Herzog, Hamburg, & Gilman, 2002). Furthermore, Keel and Klump (2003) evaluated the presence of EDs in non-Western countries and concluded that BN is a culture-bound syndrome.

Although the contribution of sociocultural factors to the pathogenesis of BN is clearly relevant, a number of studies have not corroborated the association between Western values regarding thinness and features of EDs (Byely, Archibald, Graber, & Brooks-Gunn, 2000; Cooley & Toray, 2001). In addition, much of the evidence is based on correlational analyses, which cannot rule out the possibility that individuals most dissatisfied with their bodies or wishing to be thinner may seek out particular types of media exposure (Tiggemann & Pickering, 1996). It should also be noted that ED cases have been reported throughout medical history, and although the idealisation of thinness

in women undeniably increased dramatically during the 20th century, data concerning time trends in the incidence of BN are inconclusive (see section 1.1.3.1).

1.1.5.4 Integrative theories

Although aetiological factors for BN can be categorised into distinct levels of analysis, they are not expected to operate in isolation. A complex interplay amongst the various contributors is likely (Culbert et al., 2015), and an integrated biopsychosocial understanding of the pathogenesis of BN is therefore favourable (Watkins, 2011). Culbert et al. (2015) propose a tentative model to describe the way in which biological, psychological, and sociocultural factors might intersect to increase the risk for EDs. In brief, they suggest that genetic and environmental influences, as well as neural and behavioural plasticity, determine an individual's susceptibility to the ubiquitous messages regarding the importance of being thin (Culbert et al., 2015). The model also advocates that personality traits are partially rooted in one's genes and neural circuitry, and that environmental experiences and biological vulnerabilities interact with and influence the expression of genetic risk (Culbert et al., 2015).

1.1.6 Treatment

Because BN is typically associated with marked feelings of guilt and shame regarding eating patterns, there is often a delay of many years before individuals with the disorder seek help (Fairburn & Harrison, 2003). Although the frequency of bulimic behaviours generally increases over time, most patients can be successfully treated with outpatient care, and inpatient admissions are rarely indicated (Crow & Eckert, 2016). Current National Institute for Health and Care Excellence (NICE) guidelines recommend evidence-based guided self-help programmes, cognitive behavioural therapy (CBT), and antidepressant drugs as possible first steps for treating BN (NICE, 2004). More than 40

randomised controlled trials (RCTs) have been conducted to assess treatment efficacy of psychological therapies, medications (primarily antidepressants), and combination treatments for BN (Crow & Eckert, 2016), and an overview of their findings is presented below. Nevertheless, whilst substantial evidence guides first-line treatments for BN, almost nothing is known about what approaches to try in patients who have not responded to, or been reluctant to engage in, such therapies.

1.1.6.1 Psychological interventions

CBT for BN (CBT-BN) is based on cognitive behavioural models of the disorder (see section 1.1.5.2), and is considered the best established treatment for adult sufferers (Murphy, Straebler, Cooper, & Fairburn, 2010). RCTs consistently demonstrate good outcomes, low relapse rates, and superiority to other psychological interventions; for example, the results of two meta-analyses showed that remission rates were significantly higher in patients who received CBT-BN than in both controls and those who received other forms of psychotherapy (Hay, Bacaltchuk, Stefano, & Kashyap, 2009). A new transdiagnostic 'enhanced' version of the therapy is also available, which appears better suited to patients with marked additional psychopathology of the type targeted by the treatment (Fairburn et al., 2009). Efficacious therapeutic alternatives to CBT include interpersonal therapy and Emotional Social Mind Training, which yield comparable responses of BN symptom change to individual and group CBT treatment, respectively (Fairburn et al., 1991; Lavender et al., 2012).

In recent years, successful psychological interventions for BN have been translated into guided and unguided self-help programmes delivered as bibliotherapy, CD-ROMs, or via the internet (Beintner, Jacobi, & Schmidt, 2014). These treatment options are appealing due to their cost-effectiveness (Watkins, 2011), and represent a robust means

of improving implementation and scalability of evidence-based treatment for EDs (Beintner et al., 2014). Examples of self-help programmes designed for patients with BN are Getting Better Bite by Bite (manual-based; Schmidt, Treasure, & Alexander, 2015), Overcoming Bulimia (CD-ROM-based; Schmidt et al., 2008), and Overcoming Bulimia Online (internet-based; McClay, Waters, McHale, Schmidt, & Williams, 2013). A systematic review of 50 different trials of self-help interventions for BN and BED concluded that such tools can contribute to bridging the treatment gap for these disorders, especially if they are guided by mental health specialists, and if the features of their delivery and indications are considered carefully (Beintner et al., 2014).

1.1.6.2 Pharmacological interventions

Selective serotonin reuptake inhibitors (specifically fluoxetine at doses of 60mg per day) are the drugs of first choice for the treatment of BN in terms of acceptability, tolerability and reduction of symptoms (NICE, 2004). Evidence from pharmacological trials is encouraging; for example, a large collaborative study of 398 outpatients with BN found that, compared with placebo, fluoxetine treatment resulted in greater reductions in vomiting and binge-eating episodes per week as well as an improvement in other outcome measures (Goldstein, Wilson, Thompson, Potvin, & Rampey, 1995). A systematic review of the literature concluded that, overall, fluoxetine administered for 8-16 weeks led to a significant reduction in binge-eating in the majority of studies (Shapiro et al., 2007), and data suggest that it may be a useful intervention for patients with BN who have not responded adequately to psychotherapy (Walsh et al., 2000). Nevertheless, evidence for long-term effects after treatment with medication in BN is scarce, and acceptability of pharmacotherapy is low when drugs are given alone (Treasure et al., 2010). It should be noted that fluoxetine's efficacy in treating BN is not considered a consequence of its antidepressant properties, but rather a result of the

medication's effects on satiety (Tortorella, Fabrazzo, Monteleone, Steardo, & Monteleone, 2014; Westmoreland et al., 2016).

1.1.6.3 Combined treatments

A number of studies have evaluated the efficacy of combined psychological and pharmacological interventions for individuals with BN. In a systematic review of these experiments, Hay, Claudino, and Kaio (2001) concluded that combination treatments were statistically superior to single psychotherapy but not to single antidepressants, though it was noted that the number of trials included may have been insufficient to show statistical significance in the latter comparison. Indeed, results of an earlier systematic review and meta-analysis suggested that the efficacy of combined treatments was superior to both single approaches (Bacaltchuk et al., 2000). Despite the apparent advantages of augmenting psychological interventions with pharmacological ones, data consistently show that BN patient acceptability of psychotherapy is significantly reduced with the addition of drugs (Bacaltchuk et al., 2000; Hay et al., 2001).

1.2 NEUROBIOLOGY OF BULIMIA NERVOSA

As mentioned previously, there is growing acknowledgement that neurobiological vulnerabilities make a substantial contribution to the pathogenesis of BN (Kaye, 2008). Since the human brain is often described as "the most complex structure in the universe – too complex for the human brain to understand" (Lask & Frampton, 2011), deciphering the neural mechanisms that might underpin BN has not been an easy task. Nevertheless, we now have a basic understanding of the various brain malfunctions that commonly occur in individuals with the disorder. A broad summary of the key findings relating to the neurobiology of BN is provided in this section.

1.2.1 Regulation of normal feeding behaviour

Knowledge of the regulation of normal feeding behaviour is crucial to an understanding of neurobiological dysfunction in BN and other EDs (for a detailed review see Blundell, Halford, King, & Finlayson, 2016). Food intake in healthy individuals is a complex process which can be broadly conceptualised as a 'feeding cascade' comprising three stages: (1) an appetitive phase associated with the desire to approach food that might be triggered by hunger, thirst, or a memory that a certain food tastes pleasant; (2) the motivation to approach food ('wanting'); and (3) an experience of pleasantness following ingestion ('liking') (Frank & Jappe, 2011). Based on the degree of 'liking', memories are formed that associate particular foods and environmental cues with reward, and thus initiate subsequent feeding (Frank & Jappe, 2011). The termination of eating and the prevention of further consumption are governed by a series of episodic signals that can be represented as a 'satiety cascade' (Blundell et al., 2016).

Various neurotransmitters and neuropeptides contribute to individual hunger and satiety experiences; for example, dopamine and endogenous opioids have been linked to the concepts of 'wanting' and 'liking', respectively (Kelley, Baldo, Pratt, & Will, 2005), whereas serotonin (Voigt & Fink, 2015) and acetylcholine (Avena & Rada, 2012) have been implicated in the suppression of feeding. Neuropeptide-Y and peptide YY are brain chemicals thought to stimulate eating behaviour, while cholecystokinin (a peptide hormone of the gastrointestinal system) and leptin (a hormone made by adipose tissue) appear to mediate satiety (Frank & Jappe, 2011). Brain regions involved in the regulation of feeding behaviour include the thalamus, the hypothalamus, and the nucleus accumbens (Avena & Bocarsly, 2012).

In addition to numerous biological mechanisms, emotional states have been shown to influence the regulation of non-pathological appetitive behaviour (Frank & Jappe, 2011). Indeed, Macht and Simons (2000) demonstrated that healthy females reported stronger motivations to eat during periods of negative emotions in everyday life, and the psychophysiological stress response has been found to predict increased calorie intake in a non-clinical sample (Epel, Lapidus, McEwen, & Brownell, 2001). Cognitive factors also seem to play a role; for instance, data from neurologically intact individuals suggest that representation in memory of information about a recent eating episode may be factored into decisions about how much to consume at the next meal (Higgs, 2005).

1.2.2 Neuropeptides and neuroendocrinology

Neuropeptides are small proteinaceous substances, produced and released by neurons, which act on neural substrates (Peter & Burbach, 2011). Their role in the regulation of feeding behaviour is well-documented, thus it is unsurprising that many neuropeptides appear to be altered in BN. Specifically, the disorder has been associated with elevated concentrations of neuropeptide-Y (Baranowska, Wolinska-Witort, Wasilewska-Dziubinska, Roguski, & Chmielowska, 2001), ghrelin (Monteleone, Martiadis, Fabrazzo, Serritella, & Maj, 2003), and peptide-YY (during early recovery; Kaye, Berrettini, Gwirtsman, & George, 1990), and with reduced levels of cholecystokinin (Hannon-Engel, 2012) and leptin (Jimerson, Mantzoros, Wolfe, & Metzger, 2000). Endogenous opioid levels are also low in normal-weight patients with BN (Frank & Jappe, 2011).

In addition to mediating eating behaviour, a number of neuropeptides participate in the regulation of neuroendocrine pathways; therefore, studies have evaluated the possibility that neuropeptide alterations may contribute to hormone abnormalities in BN (Bailer &

Kaye, 2003). Indeed, there appears to be a role for dysregulation in both the hypothalamic-pituitary-gonadal and -adrenal axes in the acute stage of the illness (Hildebrandt, 2013). Nevertheless, it is important to note that most of the neuropeptide and neuroendocrine alterations apparent during symptomatic episodes of BN tend to normalise after recovery, suggesting that these disturbances may be secondary to pathological eating behaviours (Bailer & Kaye, 2003; Frank & Jappe, 2011).

1.2.3 Neurotransmitters

Attempts to explain altered mood and motivational states in individuals with BN have focused on the role of monoamine neurotransmitters: the serotonergic system has received the most research attention, with some interest in the dopaminergic system (Hildebrandt, 2013). A physiological study by Jimerson and colleagues (1992) revealed lower basal cerebrospinal fluid concentrations of serotonin and dopamine metabolites in participants with BN, when compared with healthy controls. Among patients, levels of both metabolites were inversely correlated with binge-eating frequency (Jimerson et al., 1992); therefore, these neurobiological alterations may be specifically related to the core eating pathology that is characteristic of BN (Broft, Berner, Martinez, & Walsh, 2011). Reduced serotonin metabolite concentrations in cerebrospinal fluid have not only been observed in the acute symptomatic phase of illness, but also after long-term recovery from BN, suggesting that this abnormality is trait-related and contributes to the pathogenesis of the disorder (Kaye et al., 1998).

Further evidence for serotonin dysfunction in BN comes from multiple RCTs of antidepressant medications used to treat the disorder (see section 1.1.6.2). Selective serotonin reuptake inhibitors work by increasing serotonin levels in the brain, and have been shown to effectively reduce (and sometimes eliminate) binge-eating and purging

behaviours, even in BN patients who are not depressed (Crow & Eckert, 2016; Kaye et al., 2005). In recent years, additional insights into the operation of the monoamine neurotransmitter systems in BN have been gained from neuroimaging receptor studies – the results of these are discussed in section 1.2.4.3.

1.2.4 Neuroimaging

The past two decades have seen the introduction of advanced neuroimaging tools that have allowed for the *in vivo* investigation of human brain structure and function in health and disease (Frank & Jappe, 2011; Van den Eynde et al., 2012). In the field of EDs, the information gathered using neuroimaging, from individuals in both ill and recovered states, has rapidly advanced our understanding of the neurobiological underpinnings of these conditions (Frank & Jappe, 2011). Based on the scanning technique employed, brain imaging studies in BN can be divided into several categories (Kaye, 2008), and data from each of these are summarised in turn below.

1.2.4.1 Structural imaging

One of the first techniques developed for structural brain imaging was computerised tomography (CT) (Fuglset & Frampton, 2011). In the study of EDs, this medical X-ray method has enabled the assessment of overall brain structure and total brain volume (Fuglset & Frampton, 2011). Cranial CT scans performed in patients with BN have revealed ventricular enlargement and sulcal widening, indicating an overall reduction in brain volume most likely attributable to endocrine and metabolic reactions to extreme dieting (Kiriike et al., 1990; Krieg, Lauer, & Pirke, 1989). Changes in brain tissue identified by CT do not appear to have severe consequences for the cognitive status of patients with BN (Laessle, Krieg, Fichter, & Pirke, 1989).

Magnetic resonance imaging (MRI) uses powerful magnetic fields to generate high-resolution images of the structural characteristics of the brain; thus a major advantage of this neuroimaging modality over CT is that no radiation is used (Fuglset & Frampton, 2011). MRI has the potential to detect pathological changes in the brain resulting in cell loss (Whitwell, 2009). Findings of decreased cortical mass in individuals with BN were confirmed in an early MRI study, in which patients with the disorder showed cerebral atrophy (but an absence of ventricular enlargement) relative to healthy controls (Hoffman et al., 1989). More recently, BN has been associated with increased regional grey matter volumes in the orbital frontal cortex and the ventral striatum (Schafer, Vaitl, & Schienle, 2010); however, whether such differences normalise with clinical recovery is somewhat unclear (Wagner et al., 2006). Van den Eynde et al. (2012) highlight the need for collaborative multicentre efforts across the diagnostic ED spectrum, and for the assessment of longitudinal changes in brain structure following the onset of illness.

1.2.4.2 Perfusion and metabolic imaging

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) require the injection of a radioactive material and enable visualisation of brain function by measuring cerebral blood flow or metabolic rate (Fuglset & Frampton, 2011). Nozoe et al. (1995) used SPECT to show that individuals with BN had significantly higher resting-state regional cerebral blood flow in the bilateral inferior frontal and left temporal regions, in comparison to those with AN and no ED. A subsequent study found that brain perfusion in the prefrontal and parietal cortices correlated positively with body dissatisfaction and ineffectiveness in a transdiagnostic sample of patients with AN and BN (Goethals et al., 2007). Cerebral blood flow disturbances in BN are likely a state-related phenomenon, since they differ between the binge-eating and restricting phases of illness (Hirano, Tomura, Okane, Watarai, &

Tashiro, 1999) and normalise after long-term recovery (Frank et al., 2007; Frank, Kaye, Greer, Meltzer, & Price, 2000).

Data from PET imaging studies, using a radioactive isotope attached to a form of glucose, suggest that BN is associated with global and regional absolute hypo-metabolism of glucose at rest, and with low resting-state relative values of glucose metabolism in the parietal cortex (Delvenne, Goldman, De Maertelaer, & Lotstra, 1999; Delvenne, Goldman, Simon, De Maertelaer, & Lotstra, 1997). Additionally, following engagement in a neuropsychological test, individuals with BN have shown significant loss of the normal right hemisphere glucose metabolic rate exceeding the left, particularly in the temporal lobe, basal ganglia, and medial frontal structures (Hagman et al., 1990; Wu et al., 1990). Lastly, in a study by Andreason et al. (1992), participants with BN displayed a correlation between lower left anterolateral prefrontal regional cerebral glucose metabolism and greater depressive symptoms.

1.2.4.3 Receptor imaging

PET scanning is not only used to evaluate cerebral glucose metabolism – it also allows for the exploration of how other brain chemicals are processed (Fuglset & Frampton, 2011). This technology can therefore help to discover potential differences in neurotransmitter functioning between mentally ill patients and healthy controls (Fuglset & Frampton, 2011). In BN, receptor imaging studies using PET and a radioligand which binds to the serotonin 2A receptor (^{18}F-altanserin) have found that recovered patients versus healthy controls display significantly reduced binding potential in several neural regions including the medial orbitofrontal cortex (Bailer et al., 2004b; Kaye et al., 2001), which is implicated in inhibitory processes and in the representation of food-related reward (Frank & Jappe, 2011). Serotonergic disturbances in BN are not limited

to the 2A receptor: symptomatic patients have shown reduced hypothalamic and thalamic serotonin transporter availability (Tauscher et al., 2001) as well as increased serotonin 1A receptor binding, primarily in the angular gyrus, medial prefrontal cortex, and posterior cingulate cortex (Tiihonen et al., 2004).

Alterations within other neurotransmitter systems have also been reported; for example, relative to a control group, individuals with BN were found to display decreased dopamine type 2 receptor binding in two striatal sub-regions (Broft et al., 2012). In addition, BN was associated with low striatal dopamine release in the putamen (Broft et al., 2012) and with reduced μ-opioid receptor binding in the insula, which is the primary gustatory cortex (Bencherif et al., 2005). These abnormalities were negatively correlated with the frequency of binge-eating and fasting, respectively (Bencherif et al., 2005; Broft et al., 2012), suggesting that dysregulated neurotransmitter activity may contribute to the maladaptive feeding behaviours that characterise BN (Frank & Jappe, 2011).

1.2.4.4 Functional task-activation imaging

As well as generating high-resolution images depicting brain anatomy, MRI can be used to measure and map neural activity by detecting associated changes in blood oxygenation, typically in response to some form of stimulus exposure and/or neuropsychological task (Fuglset & Frampton, 2011). Known specifically as functional MRI (fMRI), this imaging technique provides a means of assessing brain dysfunction in psychiatric disorders. Results from fMRI studies in BN have been used to formulate neurocircuit-based models of illness, and are therefore discussed within this context in section 1.2.5.

1.2.5 Neurocircuitry

The brain's overall function is the result of a complicated interaction between different anatomical regions and their interconnections; thus, the diverse symptoms of BN are likely to be mediated by widespread pathological neurocircuitry. This is a view championed by the NIMH (Insel et al., 2010; Insel, 2010; Insel & Wang, 2010), and is loosely supported by neuroimaging studies in which patients with the disorder have demonstrated disturbances in blood flow, metabolic rate, and neurotransmitter functioning across numerous brain areas (see sections 1.2.4.2 and 1.2.4.3). Attempts to identify the neurocircuitry of BN have focused on systems which regulate behaviours, cognitive functions, or biological drives that are disrupted among individuals with the disorder, and evidence surrounding three major neurocircuit models of BN is considered below (key brain areas implicated are shown in Figure 1.1).

1.2.5.1 Self-regulation

Self-regulation refers to the modulation of thoughts, feelings, and actions involving deliberate as well as automated mechanisms (Karoly, 1993). It encompasses the ability to regulate emotional responses and to inhibit temptations for immediate gratification in pursuit of larger but delayed rewards (Berner & Marsh, 2014). From a clinical perspective, individuals with BN demonstrate pervasive deficits in self-regulation: a sense of 'loss-of-control' is a core feature of binge-eating (Wolfe, Baker, Smith, & Kelly-Weeder, 2009), which typically co-occurs with a host of other risky or impulsive behaviours such as substance misuse, self-harm, unprotected sex, compulsive buying, and reckless driving (Pearson et al., 2016). Furthermore, though not always consistent, neurocognitive data indicate that the condition is associated with impaired decision-making under circumstances of uncertainty, poor inhibitory control (the ability to withhold inappropriate or unwanted behaviour; Van den Eynde et al., 2011), increased

temporal discounting (the tendency to devalue delayed rewards; see chapter 4), and emotion dysregulation across multiple dimensions (Lavender et al., 2015).

The administration of neuropsychological tests in the brain scanning environment has permitted the characterisation of frontostriatal circuits that connect frontal lobe regions with the striatum and subserve the capacity for self-regulation (Berner & Marsh, 2014). These circuits comprise a portion of the broader cortico-striato-thalamo-cortical loops, which relay information from the cerebral cortex to targets in the subcortex, and then back to the original territory via direct or indirect pathways (Berner & Marsh, 2014; Marsh, Maia, & Peterson, 2009a). At least five parallel loops have been defined, initiating from and projecting back to the: (1) supplementary motor area; (2) frontal eye fields; (3) dorsolateral prefrontal cortex (DLPFC); (4) lateral orbitofrontal cortex; and (5) anterior cingulate cortex (Marsh et al., 2009a). The first three of these loops pass through the dorsal striatum and the last two pass through the ventromedial striatum, including the nucleus accumbens (Marsh et al., 2009a). Whereas the dorsal (cognitive) circuits support self-regulatory abilities, the ventral (limbic) circuits are involved in reward processing functions (Berner & Marsh, 2014; see section 1.2.5.2).

Emerging evidence from fMRI studies suggests that functional disturbances within frontostriatal networks may differentiate BN patients from healthy controls and underscore their impairments in behavioural self-regulation (i.e., their binge-eating and apparent impulsivity; Marsh et al., 2009a). Indeed, Marsh et al. (2009b) reported that, during the Simon Spatial Incompatibility task (which requires inhibiting a more automatic response in favour of a task-relevant one), women with BN responded more impulsively than healthy controls whilst failing to engage their frontostriatal circuitry appropriately (in the left inferolateral prefrontal cortex, bilateral inferior frontal gyrus,

lenticular and caudate nuclei, and anterior cingulate cortex). Reduced activation in frontostriatal systems was subsequently recorded in a similar study of bulimic adolescents, despite the finding that patients and control participants performed equally well on the task (Marsh et al., 2011).

An additional study using a Go/No-Go task to examine inhibitory motor control among female adolescents with BN or the binge-eating/purging subtype of AN also recorded abnormal frontostriatal responses in patients versus controls (e.g., in the right DLPFC and anterior cingulate cortex) in the absence of any performance disparities (Lock, Garrett, Beenhakker, & Reiss, 2011). Interestingly, however, BN was associated with increased as opposed to decreased frontostriatal activation in this instance (Lock et al., 2011). Notwithstanding this directional inconsistency, which may relate to differences in the study sample and/or neurocognitive task employed (Lock et al., 2011), taken together preliminary fMRI data implicate a role for deficient self-regulatory control circuitry in the pathophysiology of BN.

1.2.5.2 Appetite regulation and food reward processing

Since BN is predominantly characterised by aberrant feeding behaviour, and individuals with the disorder self-report an increased preference for sweet foods (Drewnowski, Bellisle, Aimez, & Remy, 1987), scientists have explored the possibility that the condition is associated with dysregulation in the neural circuitry that underpins appetite regulation and food reward processing. Brain imaging experiments have interrogated these circuits using sweet taste stimuli, and have shown that the taste pathway begins peripherally with chemoreceptors on the tongue (Kaye, Wagner, Fudge, & Paulus, 2011; Oberndorfer et al., 2013). From here, signals are transmitted through the brainstem and thalamus to the primary gustatory cortex, which includes the anterior

insula – a vital component of the ventral limbic circuitry, which supports food reward processing (Oberndorfer et al., 2013; see section 1.2.5.1). The anterior insula and associated gustatory cortex are therefore thought to respond not only to the taste and physical properties of food, but also to its rewarding value (Kaye et al., 2011). However, reward from food intake is not only experienced post-consumption; a dissociable 'mesolimbic' pathway (connecting the ventral tegmental area to the nucleus accumbens) is activated during the anticipation of palatable food rewards (Friederich, Wu, Simon, & Herzog, 2013). For this reason, the literature makes an important distinction between appetitive and consummatory reward, or wanting versus liking (Berridge, 1996).

Considerable efforts have been made to determine whether patients with BN display abnormal neural activation in response to food intake or anticipated food intake (i.e., craving), which is generally provoked by exposing participants to food-related cues (Friederich et al., 2013). In a recent systematic review of fMRI studies employing visual food stimuli, García-García et al. (2013) noted that patients with BN versus healthy controls displayed hypo-activation in the temporal lobe, inferior parietal lobule, postcentral gyrus, and visual cortex, as well as increased responses in the lateral prefrontal cortex and anterior insula. Regarding the anterior cingulate cortex, both hyper- and hypo-activation have been observed in participants with this ED (García-García et al., 2013). The authors concluded that, in BN and other EDs, images of food elicit abnormal patterns of activation in two brain circuits: (1) prefrontal areas supporting cognitive control processes; and (2) limbic and paralimbic areas associated with food reward processing (García-García et al., 2013).

Consummatory food reward has been assessed using taste experiments in bulimic patients (Friederich et al., 2013); for example, Bohon and Stice (2011) reported that women ill with BN showed trends for less activation than healthy controls in the left middle frontal gyrus, right posterior insula, right precentral gyrus, and right mid dorsal insula during receipt of a chocolate milkshake (versus tasteless solution). Furthermore, in response to simple sugars (glucose and sucrose), women recovered from BN have displayed reduced activity in the right anterior cingulate cortex and left cuneus (Frank et al., 2006), but elevated hemodynamic responses in the right anterior insula (Oberndorfer et al., 2013). High-fat taste has been associated with increased ventral striatum activation in women recovered from BN relative to those with no history of the disorder (Radeloff et al., 2014).

Evidence that BN is underpinned by dysfunction within the neural circuits that regulate appetite and food reward processing has also been obtained from neurochemical studies of humans (see section 1.2.4.3) and animal models of the disorder. Regarding the latter, findings suggest that alterations in dopamine, acetylcholine, and opioid systems in reward-related brain areas occur in response to binge-eating of palatable foods (Avena & Bocarsly, 2012). Despite the direction-of-activation discrepancies, which mirror those present in self-regulation research, the prevailing hypothesis is that individuals with BN have hypo-responsive reward circuitry, which may be compensated for by binge-eating (Friederich et al., 2013). Compared to people without an ED, patients with BN may have to eat a larger amount of appetitive food to stimulate their reward system to an equivalent extent (Friederich et al., 2013).

1.2.5.3 Body-image perception

Body image disturbance is a complex concept, which includes several psychopathological components such as overestimation of body size, body dissatisfaction, over-concern with shape and weight, and extreme reward experience when weight loss is obtained (Zanetti, Santonastaso, Sgaravatti, Degortes, & Favaro, 2013). It is influenced by perceptual and visuospatial abilities and by cognitive and affective factors relating to one's own body experience (Zanetti et al., 2013). Since distorted body image perception is a core and persisting feature of EDs, including BN, a number of fMRI studies have probed the neural correlates of this puzzling multidimensional symptom by exposing patients to body-related stimuli inside the scanner.

Interestingly, Van den Eynde et al. (2013) found that brain activation patterns in response to food cues did not differ between women with and without BN; however, when evaluating themselves against images of slim women, BN patients versus healthy controls engaged the insula more and the fusiform gyrus less, suggesting increased self-focus among individuals with BN whilst comparing themselves to a thin-ideal. Relative to healthy comparison participants, patients with the disorder have also demonstrated reduced activity in the inferior parietal lobule when viewing photographs of their own body (Vocks et al., 2010), increased medial prefrontal cortex response to images of overweight bodies (Spangler & Allen, 2012), and a reduced activation of the precuneus and middle frontal gyrus during two body image tasks (Mohr et al., 2011).

Intrinsic functional connectivity MRI has emerged as a powerful neuroimaging tool for assessing regional interactions and mapping large-scale networks in the human brain (Buckner, Krienen, & Yeo, 2013). Using this technique, Lee and colleagues (2014)

found that women with BN versus age matched healthy controls showed stronger resting-state synchrony between the dorsal anterior cingulate cortex and precuneus, which correlated with higher body shape preoccupation. Greater synchronous activity between the dorsal anterior cingulate cortex and medial orbitofrontal cortex was also observed (Lee et al., 2014). In a similar study, Lavagnino et al. (2014) reported that, relative to healthy comparison participants, those with BN had an alteration in the resting-state functional connectivity of the somatosensory cortex – a brain area implicated in body processing. Whilst available evidence indicates that body image disturbances in BN are represented at a neural level, the precise neurocircuitry involved has yet to be defined.

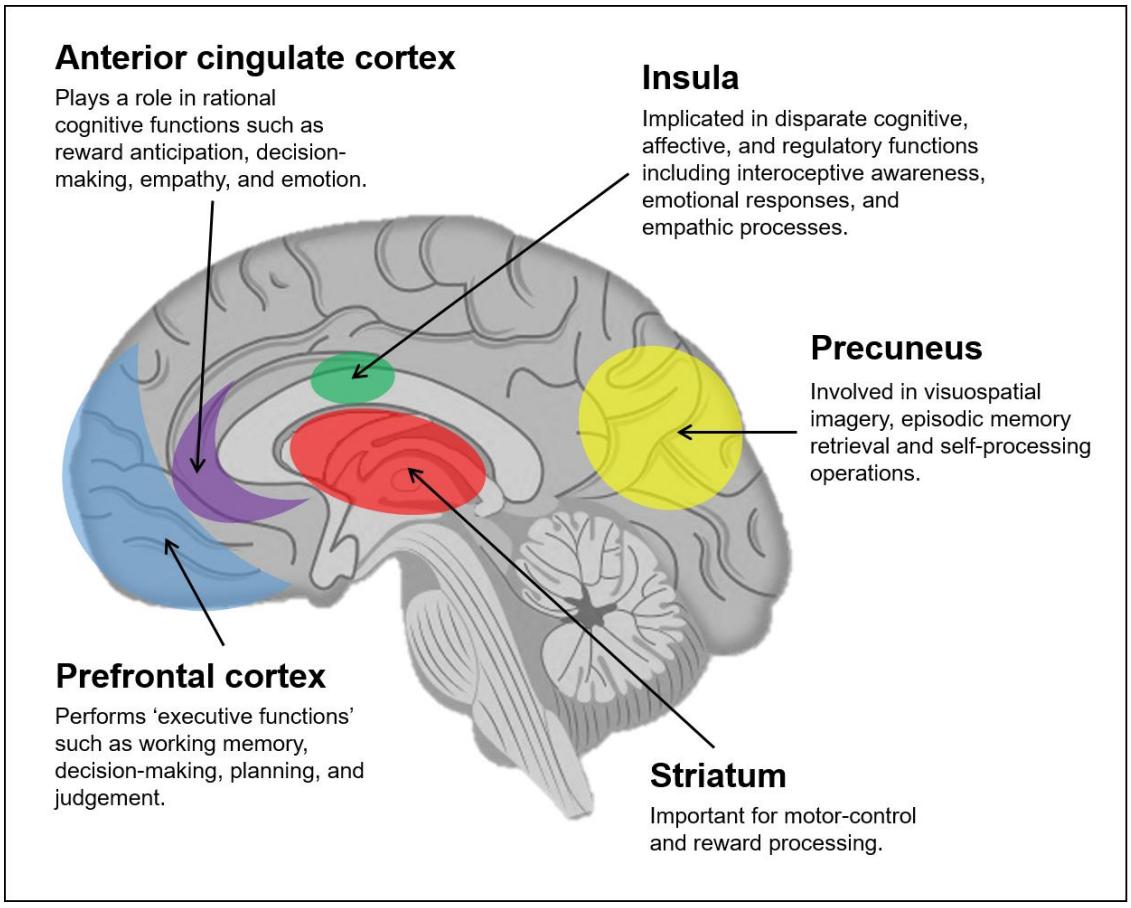


Figure 1.1 Key brain areas implicated in bulimia nervosa.

1.2.6 Comparison to other eating disorders

Individuals with EDs are currently diagnosed and treated according to readily observable symptoms, and these categorisations have dominated the research field. Although the conditions are associated with distinct clinical features (see section 1.1.2), they are all characterised by a dangerously maladaptive approach to food and, perhaps unsurprisingly, appear to be underpinned by shared neurobiological mechanisms. Most notably, there is substantial evidence that dopaminergic taste-reward pathways play a central role in the pathophysiology of all three major EDs, and alterations of the neural circuitry underlying aspects of self-regulation are also not exclusive to BN (for reviews see Avena & Bocarsly, 2012; Frank, 2015; Friederich et al., 2013; Wierenga et al., 2014). These observations have contributed to the view that EDs should be considered within a transdiagnostic framework (Brooks, Rask-Andersen, Benedict, & Schiöth, 2012; Wade, Bergin, Martin, Gillespie, & Fairburn, 2006; Waller, 2008).

1.2.7 Comparison to substance use disorders

The clinical features of BN bear significant similarities to those of drug addiction. In fact, characteristic symptoms of the ED mirror some of the *DSM-5* criteria for substance use disorder (American Psychiatric Association, 2013): people with BN report experiencing intense food cravings; food is often consumed in larger amounts than was intended; unsuccessful efforts to cut down or control one's binge-eating are commonplace; and dysregulated eating is continued despite knowledge of having a physical or psychological problem that is likely to have been caused by this behaviour. Comorbidity data are also suggestive of a strong relationship between the disorders, with the range and occurrence of substance use problems in people with BN far exceeding those in individuals with other EDs and in the general population (Woodside,

2008). Given the clinical evidence linking BN to substance use disorders, there has been extensive speculation that the conditions may share common mechanisms of neural dysfunction.

Indeed, a considerable literature shows that hyper-palatable, energy-dense foods (which are typically consumed during binge-eating episodes in BN; Rosen, Leitenberg, Fisher, & Khazam, 1986) and traditional drugs of abuse have similar effects on the human brain: they both activate dopamine and opioid neural circuitry, trigger artificially elevated levels of reward, and alter neurobiological systems (Gearhardt, Davis, Kuschner, & Brownell, 2011). Furthermore, recent experimental research in laboratory rats has revealed that sweet substances can be even more desirable than addictive drugs, and that the neural substrates of sugar may be more robust than those of cocaine (Ahmed, Guillem, & Vandaele, 2013).

Additional evidence for a shared neurobiology for BN and drug addiction comes from functional neuroimaging studies, which have demonstrated parallels across several domains; for example, there are relatively consistent findings that, like individuals with BN (see sections 1.2.4.3, 1.2.5.2, and 1.2.5.3), those with substance use disorders display reduced dopamine type 2 receptor binding in striatal regions, as well as increased prefrontal cortex activity when presented with disorder-salient stimuli (Hadad & Knackstedt, 2014). Moreover, the dorsal cognitive and ventral limbic neural circuits that appear to be disrupted in BN and other EDs are also proposed to function as key neural mechanisms underlying the altered behavioural regulation, reward processing, and cognition found in addictions (Kaye et al., 2013). Nevertheless, despite convincing support for an 'addiction model' of BN, controversy remains about whether the ED should be classified as an addictive disorder *per se* (Hadad & Knackstedt, 2014).

1.2.8 Neurobiological models

Given the breadth and complexity of brain-based aberrations that reportedly influence the pathogenesis of BN, formulating a coherent neurobiological model of illness is a challenging endeavour. Recent attempts have focused largely on the neurocircuitry of the disorder and have sought to integrate findings relating to dysfunctional self-regulatory and food reward systems (see sections 1.2.5.1 and 1.2.5.2). For example, Wierenga et al. (2014) posit that eating pathology in BN and other EDs emerges from an altered balance between inhibitory control and reward processing that is driven by changes in the dorsal and ventral neural circuitry supporting these constructs.

Similarly, Berner and Marsh (2014) contend that functional disturbances in frontostriatal circuits arise early in adolescence and contribute to an impaired capacity for self-regulatory control, which interacts with hunger to release eating behaviour from regulatory control. Aesthetic ideals of thinness then promote compensatory behaviours, which are intended to counteract weight gain (Berner & Marsh, 2014). Dysregulated frontostriatal circuits are also hypothesised to promote abnormal reward-based learning functions, which alter the processing of food rewards and allow binge-eating behaviours to solidify as 'habits' (Berner & Marsh, 2014). The authors point out that negative affect may be involved in BN pathophysiology; indeed, negative mood has been shown to diminish self-regulatory control processes (Heatherton & Wagner, 2011) and to alter the reward value of food (Bohon & Stice, 2012; Wagner, Boswell, Kelley, & Heatherton, 2012). A schematic representation of this neurobiological model, adapted from the original version (see Appendix H.1), is provided in Figure 1.2.

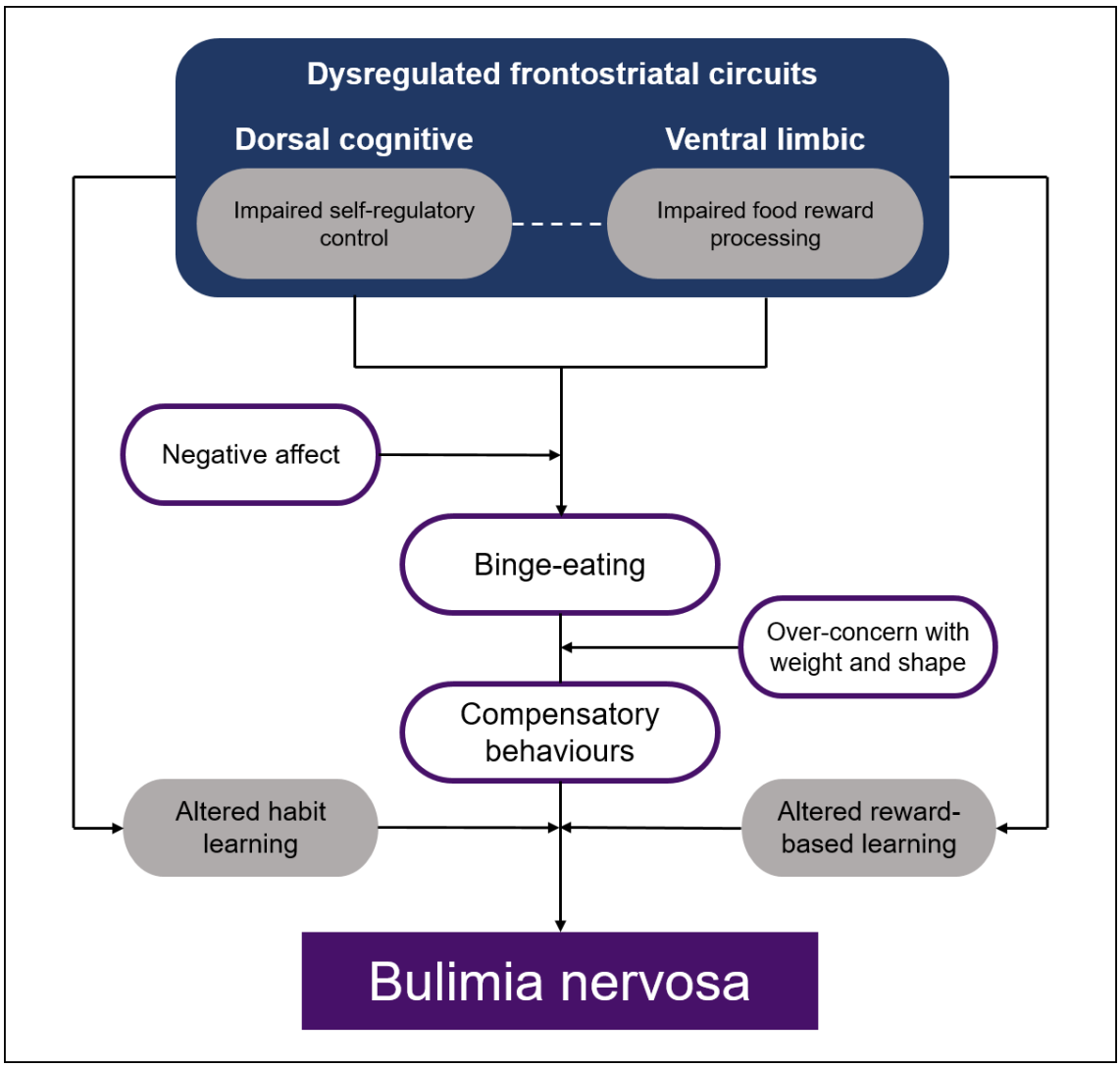


Figure 1.2 Neurobiological model of bulimia nervosa (BN), adapted from Berner and Marsh (2014).

Dysregulated overlapping dorsal cognitive and ventral limbic frontostriatal neurocircuits contribute to impaired self-regulatory control and food reward processing, respectively. The combination of these behavioural maladies leads to binge-eating, which is made more likely by negative affect. Compensatory behaviours, intended to prevent weight gain, ensue due to an over-concern with body weight and shape. This cycle is repeated and maintained as a result of altered habit learning processes caused by disturbances in frontostriatal circuitry, ultimately contributing to the development of BN.

Viewing disordered eating from this perspective provides a foundation for developing more specific and effective interventions for BN (Wierenga et al., 2014). Indeed, Berner and Marsh (2014) conclude that non-invasive brain stimulation techniques, such as tDCS and transcranial magnetic stimulation (TMS), capable of enhancing frontostriatal function may hold promise as treatments for the disorder.

1.3 TRANSCRANIAL DIRECT CURRENT STIMULATION

tDCS is a form of non-invasive neuromodulation with wide ranging potential applications in restoring impaired neural function (prosthetics), as a novel form of medical treatment (therapy), and as a tool for investigating neurons and neural function (research) (Luan, Williams, Nikolic, & Constandinou, 2014). Here, an overview of the technique is provided in relation to its role as an emerging therapeutic tool in psychiatry. The results of studies investigating the clinical efficacy of tDCS in patients with mental disorders are reviewed in chapter 2.

1.3.1 History

The effects of uncontrolled electrical stimulation on the brain have been reported since the distant past: as early as the first century, Romans used strong electric currents from live torpedo fish to treat headaches and, in the 11th century, electric catfish were suggested for the treatment of epilepsy (Brunoni et al., 2012; Williams & Fregni, 2009). With the introduction of the voltaic pile in the 1700s (the first electrical battery that could continuously provide an electric current to a circuit), it became possible to evaluate the effects of transcranial stimulation experimentally and, during the following two centuries, many researchers used galvanic current in an attempt to treat melancholia and various mental disorders (Brunoni et al., 2012). In the 1960s, data from animal

experiments showed that weak electrical currents can produce changes in spontaneous neural activity which persist for hours after the end of stimulation (Bindman, Lippold, & Redfearn, 1964; Purpura & McMurtry, 1965); nevertheless, interest in the field subsequently diminished due to the increasing popularity of electroconvulsive therapy and psychopharmacologic drugs (Brunoni et al., 2012).

A reappraisal of tDCS took place at the turn of the 21st century (Brunoni et al., 2012), when researchers learnt that the application of weak direct currents through the intact scalp could effectively influence the human brain, and that the strength, duration, and direction of changes in cortical excitability could be controlled by altering the stimulation parameters (Nitsche & Paulus, 2000; Priori, Berardelli, Rona, Accornero, & Manfredi, 1998). This discovery led to a rapidly growing literature on the therapeutic potential of tDCS in individuals with psychiatric disorders (see chapter 2).

1.3.2 Operation

tDCS uses a weak continuous electric current applied through scalp electrodes to inject currents into the brain and modulate spontaneous neuronal activity in a painless manner (Williams & Fregni, 2009). Two electrodes are typically placed over two different brain regions, though one can be positioned extracephalically, and connected to a battery source (Figure 1.3). The current enters the brain from the anode (the positively charged electrode), travels through the intervening tissue, and exits via the cathode (the negatively charged electrode; George & Aston-Jones, 2010).[6] In monkeys,

[6] Conflicting information has been published regarding the direction of current flow during tDCS, with some papers reporting that the current flows in the opposite direction – from the cathode to the anode (Nitsche et al., 2008; Williams & Fregni, 2009).

approximately 50% of the transcranially applied current successfully passes through the skull (Rush & Driscoll, 1968), and this estimate has been confirmed in humans (Dymond, Coger, & Serafetinides, 1975). Most studies use surface conductive rubber electrodes sized between 25 and 35cm^2, placed in saline-soaked cotton or sponge (Stagg & Nitsche, 2011). Currents vary between 1 and 2mA in intensity (resulting in charge densities of 343-960 C/m^2) and are commonly applied for durations of 10-20 minutes (Stagg & Nitsche, 2011).

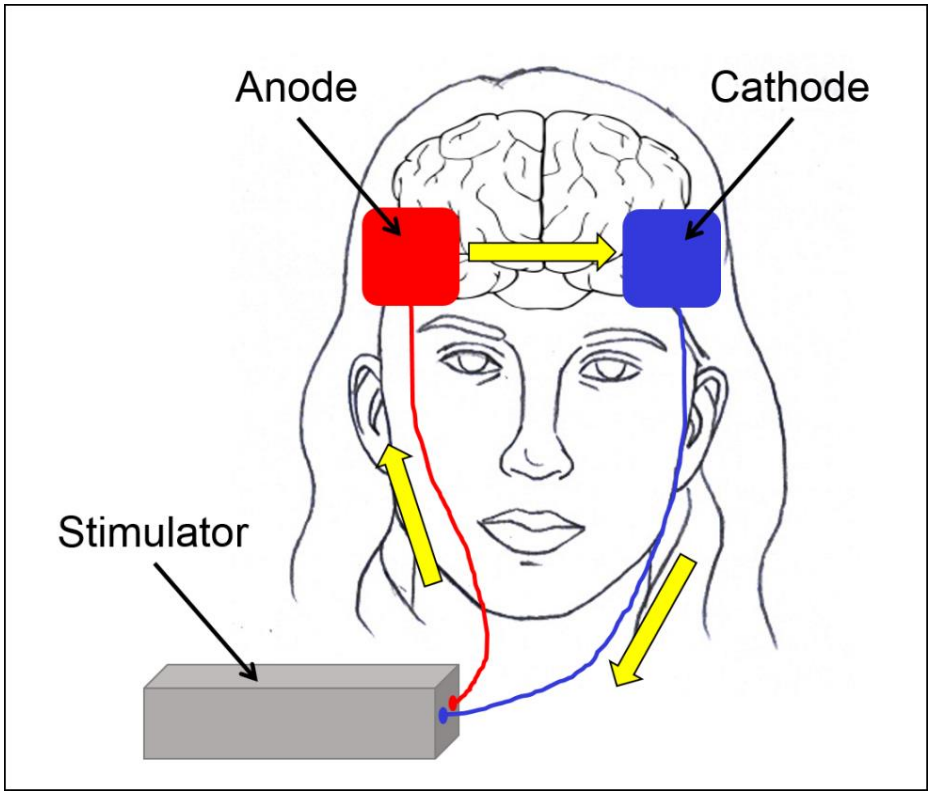


Figure 1.3 Illustration showing transcranial direct current stimulation application.

Note: the yellow arrows indicate the direction of current flow.

1.3.3 Physiological effects and mechanism of action

The precise physiological mechanisms that underlie the observed clinical responses to tDCS in psychiatric disorders (see chapter 2) are not fully understood; however, a

number of human, animal, and cell-culture studies have sought to elucidate the processes involved. Evidence shows that, at cellular level, tDCS induces focal, polarity-specific shifts in resting membrane potentials and consequent alterations in spontaneous cerebral excitability and activity via the regulation of ion channels (e.g., sodium and calcium; Nitsche et al., 2003a). It is generally accepted that anodal stimulation causes tonic depolarisation, enhanced excitability, and increased firing rates, whilst cathodal tDCS has the reverse effect, though the direction of cortical modulation depends strictly on the spatial orientation of axons and dendrites in the induced electrical field and on the intensity of the current applied (Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010).

Changes in neuronal membrane potentials are thought to account primarily for the intra-stimulation and short-term effects of tDCS; however, a single session can elicit prolonged effects which outlast the period of stimulation for up to 2 hours (Alonzo, Brassil, Taylor, Martin, & Loo, 2012) and cannot be attributed to polarisation mechanisms. Evidence suggests that these after-effects are associated with synaptic modulation and share some features with NMDA receptor-dependent long-term potentiation and depression (Nitsche et al., 2003a), which are well-characterised phenomena of neuroplasticity. A non-synaptic mechanism of action has also been proposed: this involves alterations in neuronal membrane function caused by either transmembrane protein migration or by changes in intracellular pH (Ardolino, Bossi, Barbieri, & Priori, 2005).

The physiological effects of tDCS are not confined to the area of the brain beneath the electrodes; sustained and widespread changes to cerebral activity in remote cortical and subcortical structures and alterations in functional connectivity between these regions have also been observed (DaSilva et al., 2012; Mangia, Pirini, & Cappello, 2014;

Polania, Paulus, Antal, & Nitsche, 2011; Polania, Paulus, & Nitsche, 2012). These network consequences of stimulation are likely to be key mechanistic contributors to the therapeutic effects of tDCS in psychiatry (see chapter 2), since disturbed interactions among brain regions are associated with most mental disorders (Sporns, 2013). Nevertheless, little is known about the specific physiological effects of tDCS applied to clinically relevant anatomical sites (e.g., the DLPFC), because studies investigating the neurobiological effects of stimulation have predominantly targeted the motor cortex.

1.3.4 Safety

When administered at intensities of up to 2mA for durations of approximately 20 minutes, tDCS is considered a safe neuromodulatory technique (Utz, Dimova, Oppenländer, & Kerkhoff, 2010). Indeed, the charge density typically applied in humans is two orders of magnitude lower than the experimentally determined threshold estimate in rats (Liebetanz et al., 2009), and pathological consequences in human participants have been ruled out by electroencephalography (Iyer et al., 2005), skin temperature measurements (Nitsche & Paulus, 2000), oedemasensitive magnetic resonance tomography scanning (Nitsche et al., 2004), and normal neuron specific enolase values (Nitsche et al., 2003b).

tDCS is generally well-tolerated and is associated with relatively minor, benign, and transient side effects. Although seizure is a potential risk of stimulation, no such incidences have been recounted to date (Bikson et al., 2016) and, while tDCS application has led to skin burns on rare occasions (Palm et al., 2009), this appears to occur only when standard procedures are not followed (Fregni et al., 2015). Poreisz and colleagues (2007) summarised the partially adverse effects of 567 tDCS sessions and found that a mild tingling sensation was the most commonly reported experience (noted

by 70.6% of participants). Other side effects included moderate fatigue (35.3%), a light itching sensation under the electrodes (30.4%), a headache (11.8%), and nausea (2.9%) (Poreisz et al., 2007). Nevertheless, such data should be interpreted with caution since there is evidence of selective reporting of adverse treatment effects in a large number of tDCS studies (Brunoni et al., 2011).

Whilst there is general consensus regarding the safety of particular tDCS parameters, and specific exclusion criteria are ordinarily applied to studies involving human participants (e.g., pregnancy, history of epilepsy[7], medications which decreased seizure threshold), there remains a lack of any clarity on international regulatory pathways and clear guidelines about the standard tDCS application protocols are still needed (Fregni et al., 2015).

1.3.5 Comparison to other neuromodulation modalities

tDCS is one of several neuromodulation modalities capable of influencing neural activity without the need for any invasive surgical procedures. Of these techniques, tDCS and TMS are the most commonly employed. During TMS, a figure-of-eight coil placed on the scalp generates an electrical field in the underlying cortex via electromagnetic induction (McClelland, Bozhilova, Campbell, & Schmidt, 2013), which depolarises neurons and triggers action potentials (Di Lazzaro et al., 2004). Pulses of TMS can be applied at varying intensities and in single pulses or in repetitive trains (rTMS) of high or low frequency: the choice of stimulation parameters defines whether the effects are excitatory or inhibitory (O'Shea & Walsh, 2007). Other non-invasive

[7] With the exception of studies of tDCS in epilepsy.

neuromodulation modalities, which have gained interest in recent years, are transcranial alternating current stimulation and transcranial random noise stimulation.

tDCS presents several practical advantages over TMS, such as the small size of the apparatus – allowing portability – and the possibility of simultaneously increasing and decreasing neuronal activity in two different areas of the cortex (Williams & Fregni, 2009). It is also easier to administer and significantly less expensive due to the simplicity of the device: a stimulator can cost less than £75 if manufactured locally (Fregni, Boggio, Nitsche, & Pascual-Leone, 2005). Lastly, in clinical trials the effects of tDCS can be controlled for by a sham (placebo) method that participants cannot distinguish from real stimulation (Kekic et al., 2014).

1.3.6 Importance as a clinical tool

Significant research efforts have been devoted to determining the therapeutic potential of tDCS in humans (Fregni et al., 2015). Although its efficacy in the treatment of BN has not been explored prior to the research presented in this thesis, data from numerous studies by international teams have repeatedly shown that tDCS interventions comprising multiple sessions can provide clinical benefits for several psychiatric disorders (see chapter 2). If further studies confirm the encouraging results, tDCS might be useful: (1) in patients who have not responded to prevailing therapies; (2) to potentiate medications or psychological treatments; or (3) as an alternative to procedures or drugs with undesirable effects (Williams & Fregni, 2009).

1.4 SUMMARY

BN is a complex disorder characterised by the concurrent presence of binge-eating and inappropriate compensatory behaviours. It most commonly begins during adolescence in females and is frequently a chronic and disabling condition associated with substantial psychological and physiological morbidity (Kaye, 2008). Although empirically supported psychological and pharmacological treatments exist for BN, recovery rates remain inadequate. During recent years, significant efforts have been made to understand the neurobiological basis of BN, and evidence suggests that it is underpinned by dysfunctional dorsal cognitive and ventral limbic frontostriatal neurocircuits, which support self-regulatory control and food reward processing capacities, respectively (Berner & Marsh, 2014; Friederich et al., 2013; Wierenga et al., 2014). tDCS is a non-invasive neuromodulatory tool capable of influencing cortical excitability and functional connectivity in the human brain, which may have clinical potential in the treatment of a variety of neuropsychiatric disorders, including BN.

1.5 AIMS AND HYPOTHESES

The overarching aim of this research was to investigate the therapeutic utility of tDCS in BN. Specifically, four major hypotheses were tested (additional hypotheses are detailed in the introductory sections of chapters 3-5):

(1) Existing literature demonstrates that tDCS induces beneficial clinical effects in several psychiatric disorders, and may therefore have therapeutic potential in BN (chapter 2).

(2) A single session of real versus sham tDCS applied to the bilateral DLPFC will temporarily reduce food craving and temporal discounting (a marker of low self-regulatory control denoting a preference towards more immediate

rewards) in healthy women with frequent food cravings – again, suggesting tDCS may have therapeutic potential in BN (chapter 3).

(3) Individuals with BN will display increased temporal discounting (i.e., poor self-regulatory control) relative to healthy comparison participants (chapter 4).

(4) A single session of real versus sham tDCS applied to the bilateral DLPFC will temporarily reduce symptoms, improve mood, alter food wanting/liking, and decrease temporal discounting (i.e., improve self-regulatory control) in individuals with BN (chapter 5).

1.6 THESIS MAP

This thesis consists of six chapters, inclusive of the present chapter. All results are presented within publications, which is reflected in the structure of the relative chapters (2-5) – each one includes an introduction explaining the background and rationale for the research, a material and methods section, an account of the results, and a discussion of the findings and their implications. Whilst the formatting of each publication has been amended to ensure stylistic consistency throughout the thesis, the body text remains unchanged[8]. PDF versions of the published articles are included in Appendix A.

Chapter 1: General introduction

This chapter provides detailed background information about the research topic. An overview of BN is presented, as well as a discussion of the neurobiological basis of the disorder, and an introduction to tDCS.

[8] Several minor additions were made post-viva to the body text in response to the joint examiners' report.

Chapter 2: A systematic review of the clinical efficacy of transcranial direct current stimulation in psychiatric disorders

As a first step towards investigating the therapeutic utility of tDCS in BN, this systematic review evaluates the clinical efficacy of the neuromodulatory technique across all mental disorders. Specifically, an up-to-date and comprehensive synthesis of the full evidence base is presented, which is inclusive of all study designs, and which uses a standardised quality assessment. The discussion contains a critical appraisal of the literature and an overview of the ethical issues surrounding the use of tDCS in psychiatry.

Chapter 3: The effects of prefrontal cortex transcranial direct current stimulation on food craving and temporal discounting in women with frequent food cravings

This chapter describes an RCT investigating the effects of a single-session of tDCS applied to the bilateral DLPFC on food craving, temporal discounting[9], and actual food consumption in healthy women with frequent food cravings. Findings relating to the potential moderating role of individual differences in temporal discounting, the success of the blinding procedure, and the tolerability/safety of tDCS are also reported. This preliminary RCT was conducted to inform the design of, and provide support for, the larger study presented in chapter 5. The sample was chosen because food craving is a prominent feature of BN (see section 1.2.7) that can be regarded as a manifestation of altered anticipatory food reward processing.

Chapter 4: Increased temporal discounting in bulimia nervosa

[9] In this chapter, temporal discounting is discussed in relation to high impulsivity (a deficiency in the self-regulation process) as opposed to low self-regulatory control.

A cross-sectional study assessing temporal discounting among individuals with BN and healthy controls is reported in this chapter. This research was conducted because the study presented in chapter 5 draws on the premise that individuals with BN have impaired self-regulatory control, and that manipulation of the neurocircuits that subserve this capacity will therefore induce therapeutic effects in this patient population.

Chapter 5: Transcranial direct current stimulation improves symptoms, mood, and self-regulatory control in bulimia nervosa: A randomised controlled trial

This chapter reports on the core study of the thesis: an RCT examining the effects of a single-session of tDCS applied to the bilateral DLPFC on symptoms, the wanting/liking of food (i.e., food reward processing), mood, and temporal discounting in patients with BN. Data concerning the role of electrode polarity, the effectiveness of the blinding procedure, and the safety, tolerability, and acceptability of tDCS are also presented.

Chapter 6: General discussion

In this final chapter, the key findings from the studies conducted for this thesis are summarised, and their implications discussed. Strengths and limitations associated with the research are considered, and future directions are suggested.

1.7 REFERENCES

Ahmed, S. H., Guillem, K., & Vandaele, Y. (2013). Sugar addiction: Pushing the drug-sugar analogy to the limit. *Current Opinion in Clinical Nutrition and Metabolic Care, 16*(4), 434-439.

Alonzo, A., Brassil, J., Taylor, J. L., Martin, D., & Loo, C. K. (2012). Daily transcranial direct current stimulation (tDCS) leads to greater increases in cortical excitability than second daily transcranial direct current stimulation. *Brain Stimulation, 5*(3), 208-213.

American Psychiatric Association. (1980). *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*. Washington DC: APA.

American Psychiatric Association. (1987). *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*. Washington DC: APA.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington DC: APA.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Washington DC: APA.

Andreason, P. J., Altemus, M., Zametkin, A. J., King, A. C., Lucinio, J., & Cohen, R. M. (1992). Regional cerebral glucose metabolism in bulimia nervosa. *The American Journal of Psychiatry, 149*(11), 1506-1513.

Arcelus, J., Mitchell, A. J., Wales, J., & Nielsen, S. (2011). Mortality rates in patients with anorexia nervosa and other eating disorders: A meta-analysis of 36 studies. *Archives of General Psychiatry, 68*(7), 724-731.

Ardolino, G., Bossi, B., Barbieri, S., & Priori, A. (2005). Non-synaptic mechanisms underlie the after-effects of cathodal transcutaneous direct current stimulation of the human brain. *The Journal of Physiology, 568*(2), 653-663.

Avena, N. M., & Bocarsly, M. E. (2012). Dysregulation of brain reward systems in eating disorders: Neurochemical information from animal models of binge eating, bulimia nervosa, and anorexia nervosa. *Neuropharmacology, 63*(1), 87-96.

Avena, N. M., & Rada, P. V. (2012). Cholinergic modulation of food and drug satiety and withdrawal. *Physiology & Behavior, 106*(3), 332-336.

Bacaltchuk, J., Trefiglio, R. P., Oliveira, I. R., Hay, P., Lima, M. S., & Mari, J. J. (2000). Combination of antidepressants and psychological treatments for bulimia nervosa: A systematic review. *Acta Psychiatrica Scandinavica, 101*(4), 256-264.

Bailer, U., de Zwaan, M., Leisch, F., Strnad, A., Lennkh-Wolfsberg, C., El-Giamal, N., . . . Kasper, S. (2004a). Guided self-help versus cognitive-behavioral group therapy in the treatment of bulimia nervosa. *International Journal of Eating Disorders, 35*(4), 522-537.

Bailer, U. F., & Kaye, W. H. (2003). A review of neuropeptide and neuroendocrine dysregulation in anorexia and bulimia nervosa. *Current Drug Targets - CNS &Neurological Disorders, 2*(1), 53-59.

Bailer, U. F., Price, J. C., Meltzer, C. C., Mathis, C. A., Frank, G. K., Weissfeld, L., . . . Kaye, W. H. (2004b). Altered 5-HT(2A) receptor binding after recovery from bulimia-type anorexia nervosa: Relationships to harm avoidance and drive for thinness. *Neuropsychopharmacology, 29*(6), 1143-1155.

Baranowska, B., Wolinska-Witort, E., Wasilewska-Dziubinska, E., Roguski, K., & Chmielowska, M. (2001). Plasma leptin, neuropeptide Y (NPY) and galanin concentrations in bulimia nervosa and in anorexia nervosa. *Neuroendocrinology Letters, 22*(5), 356-358.

Becker, A. E., Burwell, R. A., Herzog, D. B., Hamburg, P., & Gilman, S. E. (2002). Eating behaviours and attitudes following prolonged exposure to television among ethnic Fijian adolescent girls. *The British Journal of Psychiatry, 180*(6), 509-514.

Beintner, I., Jacobi, C., & Schmidt, U. H. (2014). Participation and outcome in manualized self-help for bulimia nervosa and binge eating disorder — A systematic review and metaregression analysis. *Clinical Psychology Review, 34*(2), 158-176.

Bencherif, B., Guarda, A. S., Colantuoni, C., Ravert, H. T., Dannals, R. F., & Frost, J. J. (2005). Regional μ-opioid receptor binding in insular cortex is decreased in bulimia nervosa and correlates inversely with fasting behavior. *Journal of Nuclear Medicine, 46*(8), 1349-1351.

Berkman, N. D., Lohr, K. N., & Bulik, C. M. (2007). Outcomes of eating disorders: A systematic review of the literature. *International Journal of Eating Disorders, 40*(4), 293-309.

Berner, L. A., & Marsh, R. (2014). Frontostriatal circuits and the development of bulimia nervosa. *Frontiers in Behavioral Neuroscience, 8,* 395.

Berridge, K. C. (1996). Food reward: Brain substrates of wanting and liking. *Neuroscience and Biobehavioral Reviews, 20*(1), 1-25.

Bikson, M., Grossman, P., Thomas, C., Zannou, A. L., Jiang, J., Adnan, T., . . . Woods, A. J. (2016). Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016. *Brain Stimulation, 9*(5), 641-661.

Bindman, L. J., Lippold, O. C. J., & Redfearn, J. W. T. (1964). The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. *The Journal of Physiology, 172*(3), 369-382.

Blundell, J., Halford, J., King, N., & Finlayson, G. (2016). The Regulation of Food Intake in Humans. In L. J. De Groot, P. Beck-Peccoz, & G. Chrousos (Eds.), *www.endotext.org*. Massachusetts: MDText.com, Inc.

Bohon, C., & Stice, E. (2011). Reward abnormalities among women with full and subthreshold bulimia nervosa: A functional magnetic resonance imaging study. *International Journal of Eating Disorders, 44*(7), 585-595.

Bohon, C., & Stice, E. (2012). Negative affect and neural response to palatable food intake in bulimia nervosa. *Appetite, 58*(3), 964-970.

Broft, A., Shingleton, R., Kaufman, J., Liu, F., Kumar, D., Slifstein, M., . . . Walsh, B. T. (2012). Striatal dopamine in bulimia nervosa: A PET imaging study. *International Journal of Eating Disorders, 45*(5), 648-656.

Broft, A. I., Berner, L. A., Martinez, D., & Walsh, B. T. (2011). Bulimia nervosa and evidence for striatal dopamine dysregulation: A conceptual review. *Physiology & Behavior, 104*(1), 122-127.

Brooks, S. J., Rask-Andersen, M., Benedict, C., & Schiöth, H. B. (2012). A debate on current eating disorder diagnoses in light of neurobiological findings: Is it time for a spectrum model? *BMC Psychiatry, 12*(1), 1-11.

Brunoni, A. R., Amadera, J., Berbel, B., Volz, M. S., Rizzerio, B. G., & Fregni, F. (2011). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *International Journal of Neuropsychopharmacology, 14*(8), 1133-1145.

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., . . . Fregni, F. (2012). Clinical research with transcranial direct current stimulation (tDCS): Challenges and future directions. *Brain Stimulation, 5*(3), 175-195.

Buckner, R. L., Krienen, F. M., & Yeo, B. T. T. (2013). Opportunities and limitations of intrinsic functional connectivity MRI. *Nature Neuroscience, 16*(7), 832-837.

Bulik, C. M., Tozzi, F., Anderson, C., Mazzeo, S. E., Aggen, S., & Sullivan, P. F. (2003). The Relation Between Eating Disorders and Components of Perfectionism. *The American Journal of Psychiatry, 160*(2), 366-368.

Byely, L., Archibald, A. B., Graber, J., & Brooks-Gunn, J. (2000). A prospective study of familial and social influences on girls' body image and dieting. *International Journal of Eating Disorders, 28*(2), 155-164.

Casey, B. J., Craddock, N., Cuthbert, B. N., Hyman, S. E., Lee, F. S., & Ressler, K. J. (2013). DSM-5 and RDoC: progress in psychiatry research? *Nature Reviews. Neuroscience, 14*(11), 810-814.

Chavez, M., & Insel, T. R. (2007). Eating disorders: National Institute of Mental Health's perspective. *The American Psychologist, 62*(3), 159-166.

Cooley, E., & Toray, T. (2001). Disordered eating in college freshman women: a prospective study. *Journal of American College Health, 49*(5), 229-235.

Crow, S. J., & Eckert, E. D. (2016). Anorexia nervosa and bulimia nervosa. In S. H. Fatemi & P. J. Clayton (Eds.), *The medical basis of psychiatry* (4 ed., pp. 211-228). New York: Springer.

Crow, S. J., Peterson, C. B., Swanson, S. A., Raymond, N. C., Specker, S., Eckert, E. D., & Mitchell, J. E. (2009). Increased mortality in bulimia nervosa and other eating disorders. *The American Journal of Psychiatry, 166*(12), 1342-1346.

Crowther, J. H., Armey, M., Luce, K. H., Dalton, G. R., & Leahey, T. (2008). The point prevalence of bulimic disorders from 1990 to 2004. *International Journal of Eating Disorders, 41*(6), 491-497.

Culbert, K. M., Racine, S. E., & Klump, K. L. (2015). Research Review: What we have learned about the causes of eating disorders – a synthesis of sociocultural, psychological, and biological research. *Journal of Child Psychology and Psychiatry, 56*(11), 1141-1164.

Currin, L., Schmidt, U., Treasure, J., & Jick, H. (2005). Time trends in eating disorder incidence. *The British Journal of Psychiatry, 186*(2), 132-135.

Cuthbert, B. N. (2014). The RDoC framework: Facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. *World Psychiatry, 13*(1), 28-35.

DaSilva, A. F., Mendonca, M. E., Zaghi, S., Lopes, M., Dossantos, M. F., Spierings, E. L., . . . Fregni, F. (2012). tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine. *Headache, 52*(8), 1283-1295.

Delvenne, V., Goldman, S., De Maertelaer, V., & Lotstra, F. (1999). Brain glucose metabolism in eating disorders assessed by positron emission tomography. *International Journal of Eating Disorders, 25*(1), 29-37.

Delvenne, V., Goldman, S., Simon, Y., De Maertelaer, V., & Lotstra, F. (1997). Brain hypometabolism of glucose in bulimia nervosa. *International Journal of Eating Disorders, 21*(4), 313-320.

Di Lazzaro, V., Oliviero, A., Pilato, F., Saturno, E., Dileone, M., Mazzone, P., . . . Rothwell, J. C. (2004). The physiological basis of transcranial motor cortex stimulation in conscious humans. *Clinical Neurophysiology, 115*(2), 255-266.

Drewnowski, A., Bellisle, F., Aimez, P., & Remy, B. (1987). Taste and bulimia. *Physiology & Behavior, 41*(6), 621-626.

Dymond, A. M., Coger, R. W., & Serafetinides, E. A. (1975). Intracerebral current levels in man during electrosleep therapy. *Biological Psychiatry, 10*(1), 101-104.

Epel, E., Lapidus, R., McEwen, B., & Brownell, K. (2001). Stress may add bite to appetite in women: a laboratory study of stress-induced cortisol and eating behavior. *Psychoneuroendocrinology, 26*(1), 37-49.

Fairburn, C. G., Cooper, Z., Doll, H. A., O'Connor, M. E., Bohn, K., Hawker, D. M., . . . Palmer, R. L. (2009). Transdiagnostic cognitive-behavioral therapy for patients

with eating disorders: A two-site trial with 60-week follow-up. *The American Journal of Psychiatry, 166*(3), 311-319.

Fairburn, C. G., Cooper, Z., & Shafran, R. (2003). Cognitive behaviour therapy for eating disorders: A "transdiagnostic" theory and treatment. *Behaviour Research and Therapy, 41*(5), 509-528.

Fairburn, C. G., & Harrison, P. J. (2003). Eating disorders. *The Lancet, 361*(9355), 407-416.

Fairburn, C. G., Jones, R., Peveler, R. C., Carr, S. J., Solomon, R. A., O'Connor, M. E., . . . Hope, R. A. (1991). Three psychological treatments for bulimia nervosa. A comparative trial. *Archives of General Psychiatry, 48*(5), 463-469.

Fairburn, C. G., Marcus, M. D., & Wilson, G. T. (1993). Cognitive-behavioral therapy for binge eating and bulimia nervosa: A comprehensive treatment manual. In C. G. Fairburn & G. T. Wilson (Eds.), *Binge eating: Nature, assessment and treatment*. New York: Guilford Press.

Fairburn, C. G., Peveler, R. C., Jones, R., Hope, R. A., & Doll, H. A. (1993). Predictors of 12-month outcome in bulimia nervosa and the influence of attitudes to shape and weight. *Journal of Consulting and Clinical Psychology, 61*(4), 696-698.

Favaro, A., Caregaro, L., Tenconi, E., Bosello, R., & Santonastaso, P. (2009). Time trends in age at onset of anorexia nervosa and bulimia nervosa. *Journal of Clinical Psychiatry, 70*(12), 1715-1721.

Field, A. E., Camargo, C. A., Jr., Taylor, C. B., Berkey, C. S., & Colditz, G. A. (1999). Relation of peer and media influences to the development of purging behaviors among preadolescent and adolescent girls. *Archives of Pediatric Adolescent Medicine, 153*(11), 1184-1189.

Frank, G. K. (2015). Advances from neuroimaging studies in eating disorders. *CNS Spectrums, 20*(4), 391-400.

Frank, G. K., Bailer, U. F., Meltzer, C. C., Price, J. C., Mathis, C. A., Wagner, A., . . . Kaye, W. H. (2007). Regional cerebral blood flow after recovery from anorexia or bulimia nervosa. *International Journal of Eating Disorders, 40*(6), 488-492.

Frank, G. K., Kaye, W. H., Greer, P., Meltzer, C. C., & Price, J. C. (2000). Regional cerebral blood flow after recovery from bulimia nervosa. *Psychiatry Research, 100*(1), 31-39.

Frank, G. K., Wagner, A., Achenbach, S., McConaha, C., Skovira, K., Aizenstein, H., . . . Kaye, W. H. (2006). Altered brain activity in women recovered from bulimic-type eating disorders after a glucose challenge: A pilot study. *International Journal of Eating Disorders, 39*(1), 76-79.

Frank, G. K. W., & Jappe, L. M. (2011). The neurobiology of eating disorders. In Y. Latzer, J. Merrick, & D. Stein (Eds.), *Understanding eating disorders*. New York: Nova Science Publishers, Inc.

Franko, D. L., Keshaviah, A., Eddy, K. T., Krishna, M., Davis, M. C., Keel, P. K., & Herzog, D. B. (2013). A longitudinal investigation of mortality in anorexia nervosa and bulimia nervosa. *The American Journal of Psychiatry, 170*(8), 917-925.

Fregni, F., Boggio, P. S., Nitsche, M., & Pascual-Leone, A. (2005). Transcranial direct current stimulation. *The British Journal of Psychiatry, 186*(5), 446-447.

Fregni, F., Nitsche, M. A., Loo, C. K., Brunoni, A. R., Marangolo, P., Leite, J., . . . Bikson, M. (2015). Regulatory considerations for the clinical and research use of transcranial direct current stimulation (tDCS): Review and recommendations from an expert panel. *Clinical Research and Regulatory Affairs, 32*(1), 22-35.

Friederich, H.-C., Wu, M., Simon, J. J., & Herzog, W. (2013). Neurocircuit function in eating disorders. *International Journal of Eating Disorders, 46*(5), 425-432.

Fuglset, T. S., & Frampton, I. (2011). Neuroimaging. In B. Lask & I. Frampton (Eds.), *Eating disorders and the brain*. West Sussex: Wiley-Blackwell.

García-García, I., Narberhaus, A., Marqués-Iturria, I., Garolera, M., Rădoi, A., Segura, B., . . . Jurado, M. A. (2013). Neural responses to visual food cues: Insights from functional magnetic resonance imaging. *European Eating Disorders Review, 21*(2), 89-98.

Gearhardt, A. N., Davis, C., Kuschner, R., & Brownell, K. D. (2011). The addiction potential of hyperpalatable foods. *Current Drug Abuse Reviews, 4*(3), 140-145.

George, M. S., & Aston-Jones, G. (2010). Noninvasive techniques for probing neurocircuitry and treating illness: Vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). *Neuropsychopharmacology, 35*(1), 301-316.

Goethals, I., Vervaet, M., Audenaert, K., Jacobs, F., Ham, H., & Van Heeringen, C. (2007). Does regional brain perfusion correlate with eating disorder symptoms in anorexia and bulimia nervosa patients? *Journal of Psychiatric Research, 41*(12), 1005-1011.

Goldstein, D. J., Wilson, M. G., Thompson, V. L., Potvin, J. H., & Rampey, A. H., Jr. (1995). Long-term fluoxetine treatment of bulimia nervosa. Fluoxetine Bulimia Nervosa Research Group. *The British Journal of Psychiatry, 166*(5), 660-666.

Hadad, N. A., & Knackstedt, L. A. (2014). Addicted to palatable foods: Comparing the neurobiology of bulimia nervosa to that of drug addiction. *Psychopharmacology, 231*(9), 1897-1912.

Hagman, J. O., Buchsbaum, M. S., Wu, J. C., Rao, S. J., Reynolds, C. A., & Blinder, B. J. (1990). Comparison of regional brain metabolism in bulimia nervosa and affective disorder assessed with positron emission tomography. *Journal of Affective Disorders, 19*(3), 153-162.

Halmi, K. A., Agras, W., Mitchell, J., & et al. (2002). RElapse predictors of patients with bulimia nervosa who achieved abstinence through cognitive behavioral therapy. *Archives of General Psychiatry, 59*(12), 1105-1109.

Hannon-Engel, S. (2012). Regulating satiety in bulimia nervosa: the role of cholecystokinin. *Perspectives in Psychiatric Care, 48*(1), 34-40.

Hastings, T., & Kern, J. M. (1994). Relationships between bulimia, childhood sexual abuse, and family environment. *International Journal of Eating Disorders, 15*(2), 103-111.

Hay, P. P., Bacaltchuk, J., Stefano, S., & Kashyap, P. (2009). Psychological treatments for bulimia nervosa and binging. *Cochrane Database of Systematic Reviews,* (4).

Hay, P. P. J., Claudino, A. M., & Kaio, M. H. (2001). Antidepressants versus psychological treatments and their combination for bulimia nervosa. *Cochrane Database of Systematic Reviews,* (4).

Heatherton, T. F., & Wagner, D. D. (2011). Cognitive neuroscience of self-regulation failure. *Trends in Cognitive Sciences, 15*(3), 132-139.

Higgs, S. (2005). Memory and its role in appetite regulation. *Physiology & Behavior, 85*(1), 67-72.

Hildebrandt, T. (2013). Anorexia Nervosa and Bulimia. In D. W. Pfaff (Ed.), *Neuroscience in the 21st century: From basic to clinical*. New York: Springer.

Hinney, A., & Volckmar, A.-L. (2013). Genetics of eating disorders. *Current Psychiatry Reports, 15*(12), 1-9.

Hirano, H., Tomura, N., Okane, K., Watarai, J., & Tashiro, T. (1999). Changes in cerebral blood flow in bulimia nervosa. *Journal of Computer Assisted Tomography, 23*(2), 280-282.

Hoek, H. W., & van Hoeken, D. (2003). Review of the prevalence and incidence of eating disorders. *International Journal of Eating Disorders, 34*(4), 383-396.

Hoffman, G. W., Ellinwood, E. H., Jr., Rockwell, W. J., Herfkens, R. J., Nishita, J. K., & Guthrie, L. F. (1989). Cerebral atrophy in bulimia. *Biological Psychiatry, 25*(7), 894-902.

Hudson, J. I., Hiripi, E., Pope, H. G., & Kessler, R. C. (2007). The Prevalence and Correlates of Eating Disorders in the National Comorbidity Survey Replication. *Biological Psychiatry, 61*(3), 348-358.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., . . . Wang, P. (2010). Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders. *The American Journal of Psychiatry, 167*(7), 748-751.

Insel, T. R. (2010). Faulty circuits. *Scientific American, 302*(4), 44-51.

Insel, T. R., & Wang, P. S. (2010). Rethinking mental illness. *JAMA, 303*(19), 1970-1971.

Iyer, M. B., Mattu, U., Grafman, J., Lomarev, M., Sato, S., & Wassermann, E. M. (2005). Safety and cognitive effect of frontal DC brain polarization in healthy individuals. *Neurology, 64*(5), 872-875.

Jacobi, C., Hayward, C., de Zwaan, M., Kraemer, H. C., & Agras, W. S. (2004). Coming to terms with risk factors for eating disorders: Application of risk terminology and suggestions for a general taxonomy. *Psychological Bulletin, 130*(1), 19-65.

Jimerson, D. C., Lesem, M. D., Kaye, W. H., & Brewerton, T. D. (1992). Low serotonin and dopamine metabolite concentrations in cerebrospinal fluid from bulimic patients with frequent binge episodes. *Archives of General Psychiatry, 49*(2), 132-138.

Jimerson, D. C., Mantzoros, C., Wolfe, B. E., & Metzger, E. D. (2000). Decreased serum leptin in bulimia nervosa. *The Journal of Clinical Endocrinology & Metabolism, 85*(12), 4511-4514.

Kanakis, D. M., & Thelen, M. H. (1995). Parental variables associated with bulimia nervosa. *Addictive Behaviors, 20*(4), 491-500.

Karoly, P. (1993). Mechanisms of self-regulation: A systems view. *Annual Review of Psychology, 44*(1), 23-52.

Kaye, W. (2008). Neurobiology of anorexia and bulimia nervosa. *Physiology & Behavior, 94*(1), 121-135.

Kaye, W. H., Berrettini, W., Gwirtsman, H., & George, D. T. (1990). Altered cerebrospinal fluid neuropeptide Y and peptide YY immunoreactivity in anorexia and bulimia nervosa. *Archives of General Psychiatry, 47*(6), 548-556.

Kaye, W. H., Frank, G. K., Bailer, U. F., Henry, S. E., Meltzer, C. C., Price, J. C., . . . Wagner, A. (2005). Serotonin alterations in anorexia and bulimia nervosa: New insights from imaging studies. *Physiology & Behavior, 85*(1), 73-81.

Kaye, W. H., Frank, G. K., Meltzer, C. C., Price, J. C., McConaha, C. W., Crossan, P. J., . . . Rhodes, L. (2001). Altered serotonin 2A receptor activity in women who have recovered from bulimia nervosa. *The American Journal of Psychiatry, 158*(7), 1152-1155.

Kaye, W. H., Greeno, C. G., Moss, H., Fernstrom, J., Fernstrom, M., Lilenfeld, L. R., . . . Mann, J. J. (1998). Alterations in serotonin activity and psychiatric symptoms after recovery from bulimia nervosa. *Archives of General Psychiatry, 55*(10), 927-935.

Kaye, W. H., Wagner, A., Fudge, J. L., & Paulus, M. (2011). Neurocircuity of eating disorders. *Current Topics in Behavioral Neurosciences, 6*, 37-57.

Kaye, W. H., Wierenga, C. E., Bailer, U. F., Simmons, A. N., Wagner, A., & Bischoff-Grethe, A. (2013). Does a shared neurobiology for foods and drugs of abuse contribute to extremes of food ingestion in anorexia and bulimia nervosa? *Biological psychiatry, 73*(9), 836-842.

Keel, P. K., & Brown, T. A. (2010). Update on course and outcome in eating disorders. *International Journal of Eating Disorders, 43*(3), 195-204.

Keel, P. K., Dorer, D. J., Franko, D. L., Jackson, S. C., & Herzog, D. B. (2005). Postremission predictors of relapse in women with eating disorders. *The American Journal of Psychiatry, 162*(12), 2263-2268.

Keel, P. K., Gravener, J. A., Joiner, T. E., Jr., & Haedt, A. A. (2010). Twenty-year follow-up of bulimia nervosa and related eating disorders not otherwise specified. *International Journal of Eating Disorders, 43*(6), 492-497.

Keel, P. K., Heatherton, T. F., Dorer, D. J., Joiner, T. E., & Zalta, A. K. (2006). Point prevalence of bulimia nervosa in 1982, 1992, and 2002. *Psychological Medicine, 36*(1), 119-127.

Keel, P. K., & Klump, K. L. (2003). Are eating disorders culture-bound syndromes? Implications for conceptualizing their etiology. *Psychological Bulletin, 129*(5), 747-769.

Kekic, M., McClelland, J., Campbell, I., Nestler, S., Rubia, K., David, A. S., & Schmidt, U. (2014). The effects of prefrontal cortex transcranial direct current stimulation (tDCS) on food craving and temporal discounting in women with frequent food cravings. *Appetite, 78*, 55-62.

Kelley, A. E., Baldo, B. A., Pratt, W. E., & Will, M. J. (2005). Corticostriatal-hypothalamic circuitry and food motivation: Integration of energy, action and reward. *Physiology & Behavior, 86*(5), 773-795.

Keski-Rahkonen, A., Hoek, H. W., Linna, M. S., Raevuori, A., Sihvola, E., Bulik, C. M., . . . Kaprio, J. (2009). Incidence and outcomes of bulimia nervosa: a nationwide population-based study. *Psychological Medicine, 39*(5), 823-831.

Kiriike, N., Nishiwaki, S., Nagata, T., Inoue, Y., Inoue, K., & Kawakita, Y. (1990). Ventricular enlargement in normal weight bulimia. *Acta Psychiatr Scand, 82*(3), 264-266.

Krieg, J. C., Lauer, C., & Pirke, K. M. (1989). Structural brain abnormalities in patients with bulimia nervosa. *Psychiatry Research, 27*(1), 39-48.

Laessle, R. G., Krieg, J. C., Fichter, M. M., & Pirke, K. M. (1989). Cerebral atrophy and vigilance performance in patients with anorexia nervosa and bulimia nervosa. *Neuropsychobiology, 21*(4), 187-191.

Lask, B., & Frampton, I. (2011). Preface. In B. Lask & I. Frampton (Eds.), *Eating disorders and the brain* (pp. 19-55). West Sussex: Wiley-Blackwell.

Lavagnino, L., Amianto, F., D'Agata, F., Huang, Z., Mortara, P., Abbate-Daga, G., . . . Northoff, G. (2014). Reduced resting-state functional connectivity of the somatosensory cortex predicts psychopathological symptoms in women with bulimia nervosa. *Frontiers in Behavioral Neuroscience, 8,* 270.

Lavender, A., Startup, H., Naumann, U., Samarawickrema, N., Dejong, H., Kenyon, M., . . . Schmidt, U. (2012). Emotional and social mind training: A randomised controlled trial of a new group-based treatment for bulimia nervosa. *PLOS ONE, 7*(10).

Lavender, J. M., Wonderlich, S. A., Engel, S. G., Gordon, K. H., Kaye, W. H., & Mitchell, J. E. (2015). Dimensions of emotion dysregulation in anorexia nervosa and bulimia nervosa: A conceptual review of the empirical literature. *Clinical Psychology Review, 40,* 111-122.

Lee, S., Ran Kim, K., Ku, J., Lee, J.-H., Namkoong, K., & Jung, Y.-C. (2014). Resting-state synchrony between anterior cingulate cortex and precuneus relates to body shape concern in anorexia nervosa and bulimia nervosa. *Psychiatry Research: Neuroimaging, 221*(1), 43-48.

Liebetanz, D., Koch, R., Mayenfels, S., Konig, F., Paulus, W., & Nitsche, M. A. (2009). Safety limits of cathodal transcranial direct current stimulation in rats. *Clinical Neurophysiology, 120*(6), 1161-1167.

Lock, J., Garrett, A., Beenhakker, J., & Reiss, A. L. (2011). Aberrant brain activation during a response inhibition task in adolescent eating disorder subtypes. *The American Journal of Psychiatry, 168*(1), 55-64.

Luan, S., Williams, I., Nikolic, K., & Constandinou, T. G. (2014). Neuromodulation: Present and emerging methods. *Frontiers in Neuroengineering, 7*, 27.

Macht, M., & Simons, G. (2000). Emotions and eating in everyday life. *Appetite, 35*(1), 65-71.

Mangia, A. L., Pirini, M., & Cappello, A. (2014). Transcranial direct current stimulation and power spectral parameters: a tDCS/EEG co-registration study. *Frontiers in Human Neuroscience, 8*, 601.

Marsh, R., Horga, G., Wang, Z., Wang, P., Klahr, K. W., Berner, L. A., . . . Peterson, B. S. (2011). An FMRI study of self-regulatory control and conflict resolution in adolescents with bulimia nervosa. *The American Journal of Psychiatry, 168*(11), 1210-1220.

Marsh, R., Maia, T. V., & Peterson, B. S. (2009a). Functional disturbances within frontostriatal circuits across multiple childhood psychopathologies. *The American Journal of Psychiatry, 166*(6), 664-674.

Marsh, R., Steinglass, J. E., Gerber, A. J., Graziano O'Leary, K., Wang, Z., Murphy, D., . . . Peterson, B. S. (2009b). Deficient activity in the neural systems that mediate

self-regulatory control in bulimia nervosa. *Archives of General Psychiatry, 66*(1), 51-63.

McClay, C.-A., Waters, L., McHale, C., Schmidt, U., & Williams, C. (2013). Online cognitive behavioral therapy for bulimic type disorders, delivered in the community by a nonclinician: Qualitative study. *Journal of Medical Internet Research, 15*(3), e46.

McClelland, J., Bozhilova, N., Campbell, I., & 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.

Mellsop, G. W., Menkes, D. B., & El-Badri, S. M. (2007). Classification in psychiatry: Does it deliver in schizophrenia and depression? *International Journal of Mental Health Systems, 1*(1), 1-4.

Mezzich, J. E. (2002). International surveys on the use of ICD-10 and related diagnostic systems. *Psychopathology, 35*(2-3), 72-75.

Micali, N., Hagberg, K. W., Petersen, I., & Treasure, J. L. (2013). The incidence of eating disorders in the UK in 2000–2009: findings from the General Practice Research Database. *BMJ Open, 3*(5).

Mitchison, D., & Mond, J. (2015). Epidemiology of eating disorders, eating disordered behaviour, and body image disturbance in males: A narrative review. *Journal of Eating Disorders, 3*(1), 1-9.

Miyasaka, K., Hosoya, H., Sekime, A., Ohta, M., Amono, H., Matsushita, S., . . . Funakoshi, A. (2006). Association of ghrelin receptor gene polymorphism with bulimia nervosa in a Japanese population. *Journal of Neural Transmission, Vienna, 113*(9), 1279-1285.

Mohr, H. M., Röder, C., Zimmermann, J., Hummel, D., Negele, A., & Grabhorn, R. (2011). Body image distortions in bulimia nervosa: Investigating body size

overestimation and body size satisfaction by fMRI. *Neuroimage, 56*(3), 1822-1831.

Monteleone, P., Bifulco, M., Di Filippo, C., Gazzerro, P., Canestrelli, B., Monteleone, F., . . . Maj, M. (2009). Association of CNR1 and FAAH endocannabinoid gene polymorphisms with anorexia nervosa and bulimia nervosa: evidence for synergistic effects. *Genes, Brain and Behavior, 8*(7), 728-732.

Monteleone, P., Martiadis, V., Fabrazzo, M., Serritella, C., & Maj, M. (2003). Ghrelin and leptin responses to food ingestion in bulimia nervosa: implications for binge-eating and compensatory behaviours. *Psycholical Medicine, 33*(8), 1387-1394.

Muller, T. D., Greene, B. H., Bellodi, L., Cavallini, M. C., Cellini, E., Di Bella, D., . . . Hinney, A. (2012). Fat mass and obesity-associated gene (FTO) in eating disorders: evidence for association of the rs9939609 obesity risk allele with bulimia nervosa and anorexia nervosa. *Obesity Facts, 5*(3), 408-419.

Murphy, R., Straebler, S., Cooper, Z., & Fairburn, C. G. (2010). Cognitive behavioral therapy for eating disorders. *The Psychiatric Clinics of North America, 33*(3), 611-627.

Newton, J. R., Freeman, C. P., & Munro, J. (1993). Impulsivity and dyscontrol in bulimia nervosa: Is impulsivity an independent phenomenon or a marker of severity? *Acta Psychiatrica Scandinavica, 87*(6), 389-394.

NICE. (2004). Eating disorders in over 8s: management. Retrieved from https://www.nice.org.uk/guidance/cg9/chapter/1-Guidance#bulimia-nervosa

Nilsson, M., Naessen, S., Dahlman, I., Linden Hirschberg, A., Gustafsson, J. A., & Dahlman-Wright, K. (2004). Association of estrogen receptor beta gene polymorphisms with bulimic disease in women. *Molecular Psychiatry, 9*(1), 28-34.

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., . . . Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation, 1*(3), 206-223.

Nitsche, M. A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., . . . Paulus, W. (2003a). Pharmacological Modulation of Cortical Excitability Shifts Induced by Transcranial Direct Current Stimulation in Humans. *The Journal of Physiology, 553*(1), 293-301.

Nitsche, M. A., Niehaus, L., Hoffmann, K. T., Hengst, S., Liebetanz, D., Paulus, W., & Meyer, B. U. (2004). MRI study of human brain exposed to weak direct current stimulation of the frontal cortex. *Clinical Neurophysiology, 115*(10), 2419-2423.

Nitsche, M. A., Nitsche, M. S., Klein, C. C., Tergau, F., Rothwell, J. C., & Paulus, W. (2003b). Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. *Clinical Neurophysiology, 114*(4), 600-604.

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology, 527 Pt 3*, 633-639.

Nozoe, S., Naruo, T., Yonekura, R., Nakabeppu, Y., Soejima, Y., Nagai, N., . . . Tanaka, H. (1995). Comparison of regional cerebral blood flow in patients with eating disorders. *Brain Research Bulletin, 36*(3), 251-255.

O'Brien, K. M., & Vincent, N. K. (2003). Psychiatric comorbidity in anorexia and bulimia nervosa: Nature, prevalence, and causal relationships. *Clinical Psychology Review, 23*(1), 57-74.

O'Shea, J., & Walsh, V. (2007). Transcranial magnetic stimulation. *Current Biology, 17*(6), R196-R199.

Oberndorfer, T. A., Frank, G. K. W., Simmons, A. N., Wagner, A., McCurdy, D., Fudge, J. L., . . . Kaye, W. H. (2013). Altered insula response to sweet taste

processing after recovery from anorexia and bulimia nervosa. *The American Journal of Psychiatry, 170*(10), 1143-1151.

Olmsted, M. P., MacDonald, D. E., McFarlane, T., Trottier, K., & Colton, P. (2015). Predictors of rapid relapse in bulimia nervosa. *International Journal of Eating Disorders, 48*(3), 337-340.

Oxford English Dictionary. (2016). bulimia, n. Retrieved from http://www.oed.com/view/Entry/24471?redirectedFrom=bulimia+nervosa&

Palm, U., Keeser, D., Schiller, C., Fintescu, Z., Reisinger, E., Baghai, T. C., . . . Padberg, F. (2009). Transcranial direct current stimulation in a patient with therapy-resistant major depression. *World Journal of Biological Psychiatry, 10*(4 Pt 2), 632-635.

Palmer, R. (2004). Bulimia nervosa: 25 years on. *The British Journal of Psychiatry, 185*(6), 447-448.

Pearson, C. M., Pisetsky, E. M., Goldschmidt, A. B., Lavender, J. M., Wonderlich, S. A., Crosby, R. D., . . . Peterson, C. B. (2016). Personality psychopathology differentiates risky behaviors among women with bulimia nervosa. *International Journal of Eating Disorders, 49*(7), 681-688.

Peter, J., & Burbach, H. (2011). What are neuropeptides? In A. Merighi (Ed.), *Neuropeptides: Methods and protocols*. New York: Human Press.

Polania, R., Paulus, W., Antal, A., & Nitsche, M. A. (2011). Introducing graph theory to track for neuroplastic alterations in the resting human brain: A transcranial direct current stimulation study. *Neuroimage, 54*(3), 2287-2296.

Polania, R., Paulus, W., & Nitsche, M. A. (2012). Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. *Human Brain Mapping, 33*(10), 2499-2508.

Polivy, J., & Herman, C. P. (2002). Causes of eating disorders. *Annual Review of Psychology, 53*(1), 187-213.

Poreisz, C., Boros, K., Antal, A., & Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Research Bulletin, 72*(4-6), 208-214.

Priori, A., Berardelli, A., Rona, S., Accornero, N., & Manfredi, M. (1998). Polarization of the human motor cortex through the scalp. *Neuroreport, 9*(10), 2257-2260.

Purpura, D. P., & McMurtry, J. G. (1965). Intracellular activities and evoked potential changes during polarization of motor cortex. *Journal of Neurophysiology, 28*, 166-185.

Quadflieg, N., & Fichter, M. M. (2003). The course and outcome of bulimia nervosa. *European Child and Adolescent Psychiatry, 12*(1), i99-i109.

Radeloff, D., Willmann, K., Otto, L., Lindner, M., Putnam, K., Leeuwen, S. V., . . . Wagner, A. (2014). High-fat taste challenge reveals altered striatal response in women recovered from bulimia nervosa: A pilot study. *World Journal of Biological Psychiatry, 15*(4), 307-316.

Ribases, M., Gratacos, M., Fernandez-Aranda, F., Bellodi, L., Boni, C., Anderluh, M., . . . Estivill, X. (2004). Association of BDNF with anorexia, bulimia and age of onset of weight loss in six European populations. *Human Molecular Genetics, 13*(12), 1205-1212.

Ricca, V., Nacmias, B., Cellini, E., Di Bernardo, M., Rotella, C. M., & Sorbi, S. (2002). 5-HT2A receptor gene polymorphism and eating disorders. *Neuroscience Letters, 323*(2), 105-108.

Rorty, M., & Yager, J. (1996). Histories of childhood trauma and complex post-traumatic sequelae in women with eating disorders. *Psychiatric Clinics of North America, 19*(4), 773-791.

Rosen, J. C., Leitenberg, H., Fisher, C., & Khazam, C. (1986). Binge-Eating episodes in bulimia nervosa: The amount and type of food consumed. *International Journal of Eating Disorders, 5*(2), 255-267.

Rossier, V., Bolognini, M., Plancherel, B., & Halfon, O. (2000). Sensation seeking: A personality trait characteristic of adolescent girls and young women with eating disorders? *European Eating Disorders Review, 8*(3), 245-252.

Rush, S., & Driscoll, D. A. (1968). Current distribution in the brain from surface electrodes. *Anesthesia & Analgesia*, *47*(6), 717-723.

Russell, G. (1979). Bulimia nervosa: An ominous variant of anorexia nervosa. *Psychological Medicine, 9*(3), 429-448.

Schafer, A., Vaitl, D., & Schienle, A. (2010). Regional grey matter volume abnormalities in bulimia nervosa and binge-eating disorder. *Neuroimage*, *50*(2), 639-643.

Schmidt, U., Andiappan, M., Grover, M., Robinson, S., Perkins, S., Dugmore, O., . . . Williams, C. (2008). Randomised controlled trial of CD–ROM-based cognitive–behavioural self-care for bulimia nervosa. *The British Journal of Psychiatry*, *193*(6), 493-500.

Schmidt, U., & Campbell, I. C. (2013). Treatment of eating disorders can not remain 'brainless': The case for brain-directed treatments. *European Eating Disorders Review, 21*(6), 425-427.

Schmidt, U., Treasure, J., & Alexander, J. (2015). *Getting better bite by bite: A survival kit for sufferers of bulimia nervosa and binge eating disorders* (2 ed.). Oxon: Routledge.

Shapiro, J. R., Berkman, N. D., Brownley, K. A., Sedway, J. A., Lohr, K. N., & Bulik, C. M. (2007). Bulimia nervosa treatment: A systematic review of randomized controlled trials. *International Journal of Eating Disorders, 40*(4), 321-336.

Smink, F. R., van Hoeken, D., & Hoek, H. W. (2013). Epidemiology, course, and outcome of eating disorders. *Current Opinion in Psychiatry, 26*(6), 543-548.

Smink, F. R. E., van Hoeken, D., Donker, G. A., Susser, E. S., Oldehinkel, A. J., & Hoek, H. W. (2016). Three decades of eating disorders in Dutch primary care: Decreasing incidence of bulimia nervosa but not of anorexia nervosa. *Psychological Medicine, 46*(06), 1189-1196.

Smink, F. R. E., van Hoeken, D., & Hoek, H. W. (2012). Epidemiology of Eating Disorders: Incidence, Prevalence and Mortality Rates. *Current Psychiatry Reports, 14*(4), 406-414.

Spangler, D. L., & Allen, M. D. (2012). An fMRI investigation of emotional processing of body shape in bulimia nervosa. *International Journal of Eating Disorders, 45*(1), 17-25.

Sporns, O. (2013). Structure and function of complex brain networks. *Dialogues in Clinical Neuroscience, 15*(3), 247-262.

Stagg, C. J., & Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *Neuroscientist, 17*(1), 37-53.

Steiger, H., Jabalpurwala, S., Champagne, J., & Stotland, S. (1997). A controlled study of trait narcissism in anorexia and bulimia nervosa. *International Journal of Eating Disorders, 22*(2), 173-178.

Steinhausen, H.-C., & Jensen, C. M. (2015). Time trends in lifetime incidence rates of first-time diagnosed anorexia nervosa and bulimia nervosa across 16 years in a Danish nationwide psychiatric registry study. *International Journal of Eating Disorders, 48*(7), 845-850.

Steinhausen, H. C., & Weber, S. (2009). The outcome of bulimia nervosa: Findings from one-quarter century of research. *The American Journal of Psychiatry, 166*(12), 1331-1341.

Stice, E. (2002). Risk and maintenance factors for eating pathology: A meta-analytic review. *Psychological Bulletin, 128*(5), 825-848.

Stice, E., Marti, C. N., & Rohde, P. (2013). Prevalence, incidence, impairment, and course of the proposed DSM-5 eating disorder diagnoses in an 8-year prospective community study of young women. *Journal of Abnormal Psychology, 122*(2), 445-457.

Stice, E., Presnell, K., & Spangler, D. (2002). Risk factors for binge eating onset in adolescent girls: A 2-year prospective investigation. *Health Psychology, 21*(2), 131-138.

Strober, M., Freeman, R., Lampert, C., Diamond, J., & Kaye, W. (2000). Controlled family study of anorexia nervosa and bulimia nervosa: Evidence of shared liability and transmission of partial syndromes. *The American Journal of Psychiatry, 157*(3), 393-401.

Sullivan, P. F. (2005). Course and outcome of anorexia nervosa and bulimia nervosa. In C. G. Fairburn & K. D. Brownell (Eds.), *Eating disorders and obesity: A comprehensive handbook*. London: Guilford Press.

Swanson, S. A., Crow, S. J., Le Grange, D., Swendsen, J., & Merikangas, K. R. (2011). Prevalence and correlates of eating disorders in adolescents: Results from the National Comorbidity Survey Replication adolescent supplement. *Archives of General Psychiatry, 68*(7), 714-723.

Tauscher, J., Pirker, W., Willeit, M., de Zwaan, M., Bailer, U., Neumeister, A., . . . Kasper, S. (2001). [123I] beta-CIT and single photon emission computed tomography reveal reduced brain serotonin transporter availability in bulimia nervosa. *Biological Psychiatry, 49*(4), 326-332.

Tiggemann, M., & Pickering, A. S. (1996). Role of television in adolescent women's body dissatisfaction and drive for thinness. *International Journal of Eating Disorders, 20*(2), 199-203.

Tiihonen, J., Keski-Rahkonen, A., Lopponen, M., Muhonen, M., Kajander, J., Allonen, T., . . . Rissanen, A. (2004). Brain serotonin 1A receptor binding in bulimia nervosa. *Biological Psychiatry, 55*(8), 871-873.

Timimi, S. (2013). No more psychiatric labels: Campaign to abolish psychiatric diagnostic systems such as ICD and DSM (CAPSID). *Self & Society, 40*(4), 6-14.

Tortorella, A., Fabrazzo, M., Monteleone, A., Steardo, L., & Monteleone, P. (2014). The role of drug therapies in the treatment of anorexia and bulimia nervosa: A review of the literature. *Journal of Psychopathology, 20,* 50-65.

Trace, S. E., Baker, J. H., Peñas-Lledó, E., & Bulik, C. M. (2013). The genetics of eating disorders. *Annual Review of Clinical Psychology, 9*(1), 589-620.

Treasure, J., Claudino, A. M., & Zucker, N. (2010). Eating disorders. *The Lancet, 375*(9714), 583-593.

Turnbull, S., Ward, A., Treasure, J., Jick, H., & Derby, L. (1996). The demand for eating disorder care. An epidemiological study using the general practice research database. *The British Journal of Psychiatry, 169*(6), 705-712.

Tyrer, P. (2014). A comparison of DSM and ICD classifications of mental disorder. *Advances in Psychiatric Treatment, 20*(4), 280-285.

Utz, K. S., Dimova, V., Oppenländer, K., & Kerkhoff, G. (2010). Electrified minds: Transcranial direct current stimulation (tDCS) and galvanic vestibular stimulation (GVS) as methods of non-invasive brain stimulation in neuropsychology - a review of current data and future implications. *Neuropsychologia, 48*(10), 2789-2810.

Van den Eynde, F., Giampietro, V., Simmons, A., Uher, R., Andrew, C. M., Harvey, P.-O., . . . Schmidt, U. (2013). Brain responses to body image stimuli but not food are altered in women with bulimia nervosa. *BMC Psychiatry, 13*(1), 1-13.

Van den Eynde, F., Guillaume, S., Broadbent, H., Stahl, D., Campbell, I. C., Schmidt, U., & Tchanturia, K. (2011). Neurocognition in bulimic eating disorders: A systematic review. *Acta Psychiatrica Scandanavica, 124*(2), 120-140.

Van den Eynde, F., Suda, M., Broadbent, H., Guillaume, S., Van den Eynde, M., Steiger, H., . . . Schmidt, U. (2012). Structural magnetic resonance imaging in eating disorders: A systematic review of voxel-based morphometry studies. *European Eating Disorders Review, 20*(2), 94-105.

van Elburg, A., & Treasure, J. (2013). Advances in the neurobiology of eating disorders. *Current Opinion in Psychiatry, 26*(6), 556-561.

van Son, G. E., van Hoeken, D., Bartelds, A. I., van Furth, E. F., & Hoek, H. W. (2006). Time trends in the incidence of eating disorders: A primary care study in the Netherlands. *International Journal of Eating Disorders, 39*(7), 565-569.

Vocks, S., Busch, M., Gronemeyer, D., Schulte, D., Herpertz, S., & Suchan, B. (2010). Neural correlates of viewing photographs of one's own body and another woman's body in anorexia and bulimia nervosa: An fMRI study. *Journal of Psychiatry & Neuroscience, 35*(3), 163-176.

Voigt, J.-P., & Fink, H. (2015). Serotonin controlling feeding and satiety. *Behavioural Brain Research, 277,* 14-31.

Volpe, U., Tortorella, A., Manchia, M., Monteleone, A. M., Albert, U., & Monteleone, P. (2016). Eating disorders: What age at onset? *Psychiatry Research, 238,* 225-227.

Wade, T. D., Bergin, J. L., Martin, N. G., Gillespie, N. A., & Fairburn, C. G. (2006). A transdiagnostic approach to understanding eating disorders. *Journal of Nervous and Mental Disease, 194*(7), 510-517.

Wagner, A., Greer, P., Bailer, U. F., Frank, G. K., Henry, S. E., Putnam, K., . . . Kaye, W. H. (2006). Normal brain tissue volumes after long-term recovery in anorexia and bulimia nervosa. *Biological Psychiatry, 59*(3), 291-293.

Wagner, D. D., Boswell, R. G., Kelley, W. M., & Heatherton, T. F. (2012). Inducing negative affect increases the reward value of appetizing foods in dieters. *Journal of Cognitive Neuroscience, 24*(7), 1625-1633.

Waller, G. (2008). A 'trans-transdiagnostic' model of the eating disorders: A new way to open the egg? *European Eating Disorders Review, 16*(3), 165-172.

Waller, G., & Sheffield, A. (2008). Causes of bulimic disorders. *Psychiatry, 7*(4), 152-155.

Walsh, B. T., Agras, W. S., Devlin, M. J., Fairburn, C. G., Wilson, G. T., Kahn, C., & Chally, M. K. (2000). Fluoxetine for bulimia nervosa following poor response to psychotherapy. *The American Journal of Psychiatry, 157*(8), 1332-1334.

Watkins, B. (2011). Eating disorders: An overview. In B. Lask & I. Frampton (Eds.), *Eating disorders and the brain* (pp. 19-55). West Sussex: Wiley-Blackwell.

Westmoreland, P., Krantz, M. J., & Mehler, P. S. (2016). Medical complications of anorexia nervosa and bulimia. *The American Journal of Medicine, 129*(1), 30-37.

Whitwell, J. L. (2009). Voxel-based morphometry: An automated technique for assessing structural changes in the brain. *Journal of Neuroscience, 29*(31), 9661-9664.

Wierenga, C. E., Ely, A., Bischoff-Grethe, A., Bailer, U. F., Simmons, A. N., & Kaye, W. H. (2014). Are extremes of consumption in eating disorders related to an

altered balance between reward and inhibition? *Frontiers in Behavioral Neuroscience, 8*(410).

Williams, J. A., & Fregni, F. (2009). Transcranial direct current stimulation. In C. M. Swartz (Ed.), *Electroconvulsive and neuromodulation therapies*. Cambridge: Cambridge University Press.

Wolfe, B. E., Baker, C. W., Smith, A. T., & Kelly-Weeder, S. (2009). Validity and utility of the current definition of binge eating. *International Journal of Eating Disorders, 42*(8), 674-686.

Woodside, B. (2008, 10 August 2016). Substance abuse in women with bulimia nervosa. Retrieved from http://www.psychiatrictimes.com/articles/substance-abuse-women-bulimia-nervosa

Woodside, D. B., Garfinkel, P. E., Lin, E., Goering, P., Kaplan, A. S., Goldbloom, D. S., & Kennedy, S. H. (2001). Comparisons of men with full or partial eating disorders, men without eating disorders, and women with eating disorders in the community. *The American Journal of Psychiatry, 158*(4), 570-574.

World Health Organisation. (1992). *The ICD–10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: WHO.

World Health Organisation. (2016). International Statistical Classification of Diseases and Related Health Problems 10th Revision, Version: 2016. Retrieved from http://apps.who.int/classifications/icd10/browse/2016/en

Wu, J. C., Hagman, J., Buchsbaum, M. S., Blinder, B., Derrfler, M., Tai, W. Y., . . . Sicotte, N. (1990). Greater left cerebral hemispheric metabolism in bulimia assessed by positron emission tomography. *The American Journal of Psychiatry, 147*(3), 309-312.

Zaghi, S., Acar, M., Hultgren, B., Boggio, P. S., & Fregni, F. (2010). Noninvasive brain stimulation with low-intensity electrical currents: Putative mechanisms of action for direct and alternating current stimulation. *Neuroscientist, 16*(3), 285-307.

Zanetti, T., Santonastaso, P., Sgaravatti, E., Degortes, D., & Favaro, A. (2013). Clinical and temperamental correlates of body image disturbance in eating disorders. *European Eating Disorders Review, 21*(1), 32-37.

Chapter 2. A systematic review of the clinical efficacy of transcranial direct current stimulation in psychiatric disorders

---

Kekic, M., Boysen, E., Campbell, I. C., & Schmidt, U. (2016). A systematic review of the clinical efficacy of transcranial direct current stimulation (tDCS) in psychiatric disorders. *Journal of Psychiatric Research, 74,* 70-86.

2.1 ABSTRACT

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique, which can be used to selectively disrupt patterns of neural activity that are associated with symptoms of mental illness. tDCS has been implemented in numerous therapeutic trials across a range of patient populations, with a rapidly increasing number of studies being published each year. This systematic review aimed to evaluate the efficacy of tDCS in the treatment of psychiatric disorders. Four electronic databases were searched from inception until December 2015 by two independent reviewers, and 66 eligible studies were identified. Depression was the most extensively researched condition, followed by schizophrenia and substance use disorders. Data on obsessive compulsive disorder, generalised anxiety disorder, and anorexia nervosa were also obtained. The quality of included studies was appraised using a standardised assessment framework, which yielded a median score corresponding to "weak" on the three-point scale. This improved to "moderate" when case reports/series were excluded from the analysis. Overall, data suggested that tDCS interventions comprising multiple sessions can ameliorate symptoms of several major psychiatric disorders, both acutely and in the long-term. Nevertheless, the tDCS field is still in its infancy, and several methodological and ethical issues must be addressed before clinical efficacy can truly be determined. Studies probing the mechanisms of action of tDCS and those facilitating the definition of optimised stimulation protocols are warranted. Furthermore, evidence from large-scale, multi-centre randomised controlled trials is required if the transition of this therapy from the laboratory to the clinic is to be considered.

2.2 INTRODUCTION

Mental disorders constitute a major public health issue, directly accounting for 7.4% of disease burden worldwide (Murray et al., 2012) and 17.8% in the European Union (Wittchen et al., 2011). They are the leading cause of years lived with disability globally (Whiteford et al., 2013), impacting personal well-being, social relationships and work productivity, and are associated with substantial loss of quality of life (Alonso et al., 2004). Despite an increase in the rate of treatment, psychiatric morbidity has remained relatively stable over the past two decades (Kessler et al., 2005; Wittchen et al., 2011), thus there is a need to develop novel therapeutic strategies to improve clinical outcomes.

Recent advances in functional neuroimaging have facilitated an improved understanding of the disturbances in neural circuitry that underlie mental disorders (Frangou, 2014; Price & Drevets, 2013). Consequently, there has been increased interest in neuromodulation methods which can be used to selectively disrupt patterns of neural activity that are associated with symptoms of illness, with the objective of improving behavioural outcomes whilst generating information about disease mechanisms. These emerging brain-directed interventions adhere to an experimental therapeutics approach, which is now widely regarded as the gold-standard strategy for treatment-focused psychiatric research (Insel, 2014; Insel & Gogtay, 2014; Medical Research Council, 2010).

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique which delivers low-amplitude direct currents to the brain via two surface sponge electrodes (anode and cathode) attached to distinct areas of the scalp with a rubber headband (Wagner, Valero-Cabre, & Pascual-Leone, 2007). The current penetrates the skull and enters the brain from the anode, travels through the tissue, and

exits via the cathode (George & Aston-Jones, 2010). tDCS presents several practical advantages over alternative neuromodulation modalities – it has a favourable safety-feasibility profile, offers a convincing placebo, can be applied bilaterally, and is portable and inexpensive.

During the past decade, tDCS has been implemented in numerous trials across a range of patient populations and psychiatric conditions, with a rapidly increasing number of studies being published each year (Figure 2.1). This systematic review critically evaluates the clinical efficacy of tDCS in people with mental illness, and is warranted given the limited efficacy of existing therapies, the evidence that psychiatric disorders are neural circuit-based disorders that could benefit from brain-directed interventions, and the appealing characteristics of tDCS in comparison to other forms of neuromodulation. Although several reviews and meta-analyses have previously addressed this topic, the majority have either studied major depression (Berlim, Van den Eynde, & Daskalakis, 2013; Brunoni, Ferrucci, Fregni, Boggio, & Priori, 2012a; Kalu, Sexton, Loo, & Ebmeier, 2012; Meron, Hedger, Garner, & Baldwin, 2015; Shiozawa et al., 2014b) or schizophrenia alone (Mondino et al., 2015a), or used unsystematic search procedures (Brunoni et al., 2012b; Kuo, Paulus, & Nitsche, 2014; Tortella et al., 2015) which promote a number of biases (Schmidt & Gotzsche, 2005). To our knowledge, one prior publication has systematically reviewed the therapeutic effects of tDCS across all psychiatric disorders (Mondino et al., 2014). Given the high growth rate of publication in the field, we have provided an up-to-date and comprehensive synthesis of the full evidence base, which is inclusive of all psychiatric conditions and study designs, and which uses a standardised quality assessment.

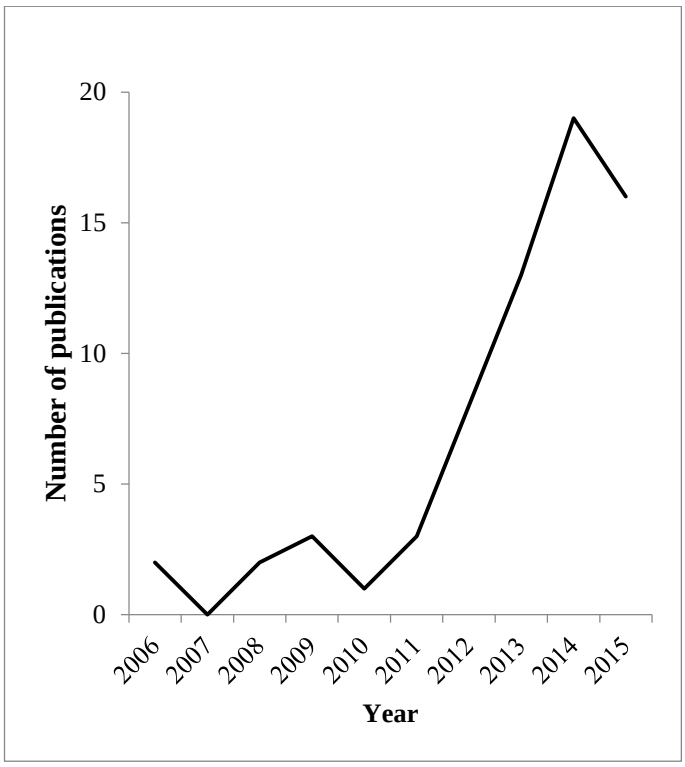


Figure 2.1 Number of publications included in this review by year between 2006 and 2015.

Note: databases were searched for papers published online or in print until 3rd December 2015.

2.3 MATERIAL AND METHODS

2.3.1 Selection criteria

Studies in English of any design that investigated the clinical efficacy of tDCS in individuals with psychiatric disorders were eligible for inclusion. Studies of participants with neurological conditions were excluded, as were those that did not report any symptom outcome variables. Publications were not restricted based on whether details of a Diagnostic and Statistical Manual of Mental Disorders/International Classification of Diseases diagnosis were given, and those involving co-interventions were eligible for inclusion if the effects of tDCS *per se* were discernible.

2.3.2 Search strategy

Four electronic databases (MEDLINE, Embase, PsycINFO, and CINAHL) were searched (via OvidSP and EBSCOhost) from inception until 3rd December 2015 using the following Medical Subject Headings and keywords: transcranial direct current stimulation, tDCS, and transcranial DC stimulation, in combination with mental disorder, mental illness, psychiatric disorder, psychiatric disease, addict*, anorexi*, anxiety disorder, auditory verbal hallucinations, bipolar disorder, bulimi*, catatonia, craving, dependence, depersonali?ation, depressi*, eating disorder, mania, obsessive compulsive disorder, OCD, panic disorder, personality disorder, phobi*, posttraumatic stress disorder, psychosis, PTSD, and schizophrenia. These searches were supplemented by internet searches and hand-searches of reference lists of relevant papers and reviews. Citation tracking in Web of Science was also performed.

Titles and abstracts of retrieved publications were imported into EndNote, duplicates were removed, and papers that were deemed highly unlikely to be relevant were disregarded. Full-text versions of the remaining articles were then obtained and screened according to the pre-specified eligibility criteria. All papers that did not meet the inclusion criteria were excluded, with the reasons documented (Figure 2.2). The entire search process was conducted independently by two reviewers (M.K. and E.B.) and disagreements at the final stage were resolved by consensus.

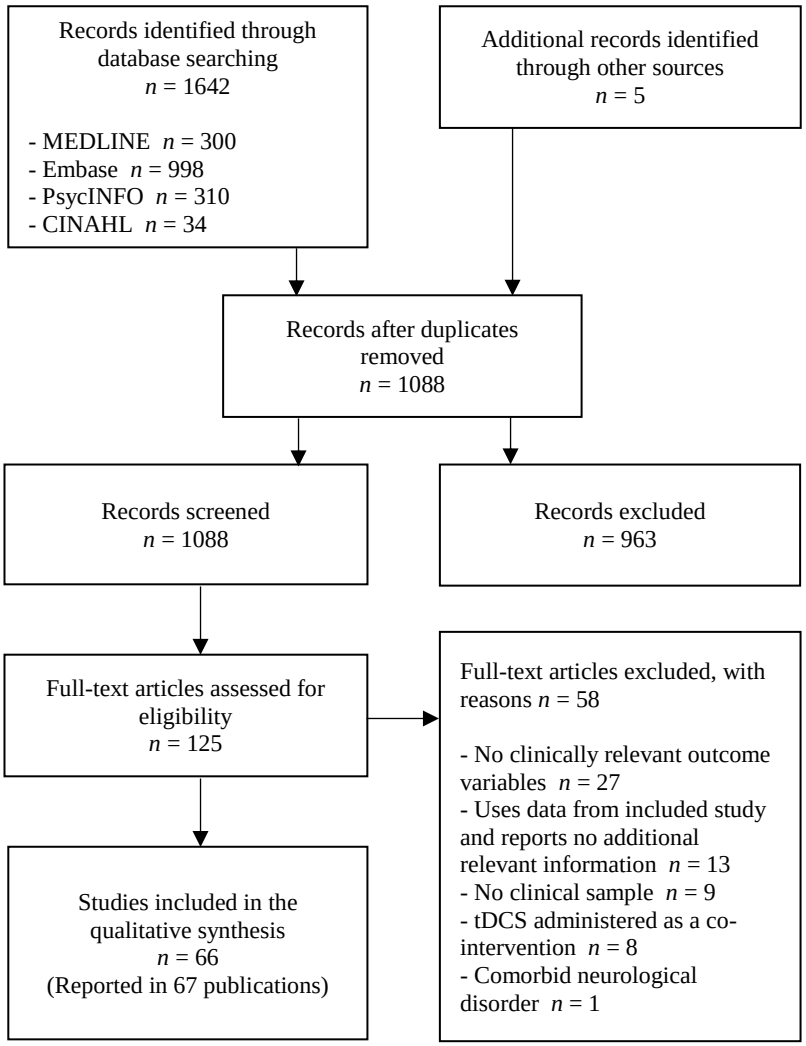


Figure 2.2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

2.3.3 Quality assessment and data extraction

The quality of included studies was appraised using a standardised evaluation framework – the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies (Thomas, Ciliska, Dobbins, & Micucci, 2004) – which is suitable for use with multiple study designs. The instrument assesses six methodological domains: selection bias, study design, confounders, blinding, data collection methods, and withdrawals and dropouts. Each component is rated as strong, moderate, or weak on a three-point scale and these scores are averaged to provide a global rating. The quality

assessment was performed independently by two reviewers (M.K. and E.B.) and discrepancies were discussed until an agreement was reached.

The principal reviewer (M.K.) extracted data from all included studies into an electronic summary table which was then checked by another reviewer (E.B.). Information collected related to patient population, sample size, study design, stimulation protocol, measurement of clinical efficacy, and relevant findings. Due to the methodological diversity of the included studies, a narrative synthesis is presented.

2.4 RESULTS

2.4.1 Characteristics of included studies

We identified 66 studies (reported in 67 publications, including data from 1021 participants) that met the inclusion criteria for this review (Figure 2.2). The majority (30 studies) evaluated the efficacy of tDCS for the treatment of major depression in patients with major depressive disorder (MDD) or bipolar disorder (BP). The remaining studies were of patients with schizophrenia (23 studies), substance use disorders (SUDs; 7 studies), obsessive compulsive disorder (OCD; 4 studies), generalised anxiety disorder (GAD; 1 study), and anorexia nervosa (AN; 1 study). There were 23 randomised controlled trials (RCTs) and 41 open-label studies (2 had blind-raters) including 24 case reports/series. In addition, there was one double-blind, sham-controlled case report and one study with a hybrid design involving both double-blind, sham-controlled and open-label conditions. All studies had adult-only samples which differed substantially in size, ranging from 1 to 120 participants (M = 18.09, SD = 19.99).

All but four of the studies had stimulation protocols comprising multiple sessions; however, the duration, number, and frequency of these sessions, as well as the tDCS parameters employed, varied considerably across trials (Tables 2.2-2.5). The unilateral or bilateral dorsolateral prefrontal cortex (DLPFC) was targeted in 59 of the 66 studies. Other hypothesis-driven sites of stimulation were the temporoparietal junction (TPJ), cerebellum, occipital lobe, orbitofrontal cortex (OFC), frontotemporal region, pre-supplementary and supplementary motor areas (pre-SMA/SMA), and Wernicke's area.

2.4.2 Quality of included studies

The median global rating derived from the EPHPP Quality Assessment Tool for Quantitative Studies was 3 (weak). Overall, the weakest scores were obtained for the selection bias component of the tool because 38% of studies were case reports/series and a further 26% did not adequately describe the participant selection process. A high number of weak ratings were also assigned for the blinding component because 62% of the studies were open-label. The strongest-scoring dimension was data collection methods because 63 of the 66 studies used at least one standardised outcome measure with known reliability and validity. Where relevant, withdrawals and dropouts were generally addressed and reported accurately, and only 5 studies had a retention rate lower than 80% at the final stage of data collection. Of the 18 studies that involved 2 or more independent experimental groups, 16 reported no baseline between-group differences with respect to important variables, 1 noted that the active group had more severe symptoms pre-tDCS, and 1 study did not provide this information. A numerical summary of the component ratings is provided in Table 2.1. Since the high proportion of case reports/series notably impacted the results of the quality assessment, average scores were calculated with and without these studies included.

Table 2.1 Median and mean component ratings from the EPHPP Quality Assessment Tool for Quantitative Studies.

Component	Ratings			
	All included studies (N = 66)		Excluding case reports/series (n = 41)	
	Median	Mean	Median	Mean
Selection Bias	3	2.65	2	2.44
Study Design	2	2.05	1	1.44
Confounders	1	1.21	1	1.21
Blinding	3	2.24	1	1.83
Data Collection Methods	1	1.08	1	1.12
Withdrawals and Dropouts	1	1.23	1	1.23
Global Rating	3	2.35	2	1.93

2.4.3 Study findings

2.4.3.1 Major depression

A number of studies have provided evidence that unilateral DLPFC stimulation (anodal tDCS to the left DLPFC [l-DLPFC], cathodal tDCS to a contralateral intra- or extra-cephalic region) can ameliorate symptoms of major depression (Table 2.2). The earliest of these were conducted by Fregni and colleagues (Fregni et al., 2006a; Fregni, Boggio, Nitsche, Rigonatti, & Pascual-Leone, 2006b) who found that five sessions of sham-controlled tDCS induced significant improvements in mood (indexed by the Hamilton Rating Scale for Depression [HRSD] and the Beck Depression Inventory [BDI]) in two small samples of MDD patients (N = 10, N = 18). Their findings were later extended by Boggio et al. (2008a) who demonstrated that, in 40 MDD patients, 10 sessions of anodal tDCS to the l-DLPFC led to persisting reductions in HRSD and BDI scores when compared with both sham tDCS and an active control (anodal tDCS to the occipital cortex). Lasting improvements in depressive symptoms following 10 sessions of anodal

l-DLPFC tDCS were also recorded in 8 HIV-MDD co-diagnosed individuals (Knotkova et al., 2012) and one 92-year-old MDD patient (Shiozawa et al., 2014a).

Other studies of anodal tDCS to the l-DLPFC in major depression have yielded less encouraging results. For example, Palm et al. (2009) reported that 16 sessions of tDCS did not exert a meaningful therapeutic effect in a patient with treatment-resistant MDD, and Wolkenstein and Plewnia (2013) recorded no tDCS-related changes in positive or negative affect (indexed by the Positive and Negative Affect Schedule [PANAS]) in 22 MDD patients following real versus sham tDCS (though a single session protocol was used). More ambiguous findings have also been documented: a 2-week course of sham-controlled tDCS had no effect on clinical depression ratings (HRSD, BDI) but increased subjectively-rated positive emotions (according to the PANAS) in 22 participants with refractory MDD (n = 20) or BP (n = 2) (Palm et al., 2012). Similarly, whilst 10 sessions of sham-controlled twice-daily tDCS did not alleviate symptoms in 23 patients with treatment-resistant MDD (indexed by the HRSD, BDI, and Montgomery-Åsberg Depression Rating Scale [MADRS]), more participants in the active tDCS group met the response and remission criteria immediately, 12 days, and 30 days after treatment (Bennabi et al., 2015).

In a parallel group RCT conducted by Loo et al. (2010), comparable reductions in depression severity (HRSD, MADRS) occurred following 5 sessions of real and sham anodal l-DLPFC tDCS in 35 patients with MDD. Although the authors later recorded a reduction in MADRS scores in 58 MDD/BP patients following 15 sessions of sham-controlled tDCS, this result was clinically modest, the differences did not reach significance on any other mood outcome measures, and an equal number of participants in the active and sham groups met the response and remission criteria (Loo et al., 2012).

Nevertheless, a between-group difference in the proportion of responders became apparent after participants (n = 52) received an additional 15 sessions of open-label active tDCS: at 1-week and 1-month follow-ups, responder rates were superior in the group that had received active treatment throughout (Loo et al., 2012). Interestingly, 11 participants who showed an inadequate response to, or relapsed following, 3 weeks of active tDCS treatment in this study (Loo et al., 2012) subsequently displayed moderate clinical improvements after 20 further sessions of open-label tDCS in which the cathode was placed extracephalically (over the right upper arm) instead of over the right lateral orbit (Martin et al., 2011). Those who met the criterion for response (n = 7), and 19 responders from the original study (Loo et al., 2012), then received 6 months of weekly/fortnightly continuation tDCS and data indicated that the cumulative probability of surviving without relapse was 84% at 3 months and 51% at 6 months (Martin et al., 2013).

In contrast to those described above, a number of studies investigating the effects of tDCS in major depression have used bilateral DLPFC modulation (anodal left/cathodal right). For example, Ferrucci et al. (2009b) administered 10 sessions of twice-daily open-label tDCS to 14 patients with severe, drug-resistant MDD and observed mood improvements (HRSD, BDI, self-report visual analogue scales [VASs]) which persisted for at least 1 month after the end of treatment. Similarly, Dell'Osso et al. (2012) delivered tDCS at the same parameters to 23 poor-responder depressed patients (MDD = 15, BP = 8) and noted a clinical benefit that was maintained for at least 3 months in half of the sample (Dell'Osso et al., 2014). This protocol (10 sessions of twice-daily open-label tDCS) was adopted by three further studies which explored the comparative benefits of tDCS in patients with differing clinical profiles (Brunoni et al., 2013a; Brunoni et al., 2011b; Ferrucci et al., 2009a). Robust and persisting improvements in

depressive symptoms were recorded across a total of 145 individuals with MDD (*n* = 112) or BP (*n* = 33) (Brunoni et al., 2013a; Brunoni et al., 2011b; Ferrucci et al., 2009a), and whilst the treatment appeared to be equally effective for patients regardless of their diagnosis (Brunoni et al., 2013a; Brunoni et al., 2011b), a better response was seen in participants with severe MDD than in those with mild/moderate MDD (Ferrucci et al., 2009a). Interactions between tDCS and drug therapy were also reported: whereas benzodiazepine use was associated with a worse outcome, antidepressants generally increased the beneficial effects of tDCS (Brunoni et al., 2013a).

Evidence from a multi-phase trial by Brunoni et al. (2013b) supports the finding that bilateral DLPFC tDCS has greater efficacy when administered with antidepressants. During phase I, 120 patients with MDD were assigned to 1 of 4 groups: sham tDCS/placebo pill (placebo), sham tDCS/sertraline (sertraline-only), active tDCS/placebo pill (tDCS-only), or active tDCS/sertraline (combined treatment) (the tDCS intervention consisted of 10 consecutive weekday sessions followed by 2 extra sessions every other week) (Brunoni et al., 2013b). On the basis of MADRS scores, tDCS-only was more effective than placebo, but the combined treatment was superior to all other groups (Brunoni et al., 2013b). In phase II of the trial, willing non-responders who received sham tDCS in phase I (*n* = 23) underwent 10 sessions of active tDCS and moderate improvements in depressive symptomology were observed (Valiengo et al., 2013). During phase III, active tDCS responders from phase I and II (*n* = 42) received 24 weeks of maintenance treatment and continued to respond for an average of 11.7 weeks (Valiengo et al., 2013).

Less promising results were obtained by Blumberger, Tran, Fitzgerald, Hoy, and Daskalakis (2012), who found that 15 sessions of sham-controlled bilateral DLPFC

tDCS did not lower HRSD scores in 24 patients with treatment-resistant MDD. Additionally, Shiozawa, da Silva, and Cordeiro (2015) described a patient – with inferred right hemispheric dominance – whose depressive symptoms intensified (according to HRSD scores) following five sessions of anodal left/cathodal right DLPFC tDCS. Brunoni et al. (2014a) showed that in 37 MDD patients, active tDCS (10 sessions) combined with cognitive control therapy (CCT) was not superior to sham tDCS combined with CCT. This is in contrast to a study by Segrave, Arnold, Hoy, and Fitzgerald (2014), in which concurrent CCT potentiated antidepressant outcomes (MADRS, BDI) from anodal l-DLPFC tDCS (the cathode was placed over the right lateral orbit). D'Urso, Mantovani, Micillo, Priori, and Muscettola (2013) also described the effects of adjunctive tDCS and cognitive therapy: in a patient with refractory MDD, the therapeutic response to 10 sessions of bilateral DLPFC tDCS (indexed by the HRSD) was substantially more enduring when the treatment was coupled with weekly cognitive behavioural therapy (CBT).

To date, two studies using tDCS to treat major depression have targeted an alternative site to the DLPFC. In these open-label trials, improvements in symptoms (indexed by the MADRS) were observed following modulation of the fronto-occipital (Ho et al., 2014) or -temporal regions (Ho et al., 2015) (20 sessions) in a total of 18 patients with MDD.

Table 2.2 Studies in patients with major depression (in chronological order).

			Design		Stimulation protocol for experimental condition(s)							
Study	*N* [a]	Diagnosis	Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency	Outcomes extracted for this review	Findings	Comments
Fregni et al. (2006a)	10	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supraorbital area	1	35	20 mins, 5 sessions (1 per day for 5 alternate days)	HRSD, BDI	Improvement in depressive symptoms after active versus sham tDCS.	No mention of DSM/ICD diagnosis.
Fregni et al. (2006b)	18	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supraorbital area	1	35	20 mins, 5 sessions (1 per day for 5 alternate days)	HRSD	Improvement in depressive symptoms after active versus sham tDCS.	No mention of DSM/ICD diagnosis.
Boggio et al. (2008a)	40	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS of the DLPFC; (ii) tDCS of the occipital cortex (active control);	Left DLPFC	Right supraorbital area	2	-	20 mins, 10 sessions (1 per weekday for 2 consecutive weeks)	HRSD-21, BDI	Improvement in depressive symptoms after tDCS to the DLPFC versus sham tDCS and tDCS to the occipital cortex, maintained for at least 1 month.	

Study	*N* [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
				(iii) sham tDCS								
Ferrucci et al. (2009b)	14	MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	32	20 mins, 10 sessions (2 per day for 5 consecutive days)	BDI, HRSD, self-reported mood (VAS)	Improvement in depressive symptoms post-tDCS, maintained for at least 1 month.	
Ferrucci et al. (2009a)	32	MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	-	20 mins, 10 sessions (2 per day for 5 consecutive days)	HRSD, BDI	Improvement in depressive symptoms post-tDCS, particularly in patients with severe depression who maintained improvements for at least 1 month.	

Study	*N* [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
Palm et al. (2009)	1	MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right supraorbital area	1	35	20 mins, 16 sessions (1 per day then 2 per day over 27 days)	BDI, HRSD, CGI	Improvement in depressive symptoms post-tDCS, but no change in CGI score.	
Loo et al. (2012)	35	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right lateral orbit	1	35	20 mins, 5 sessions (1 per day for 5 alternate weekdays) plus 5 further sessions (active for both groups) at the same treatment frequency	MADRS, HRSD, CGI-S, BDI, PGI-I	No improvement in depressive symptoms after active versus sham tDCS.	Sessions 6-10 were active for all participants, but they were not made aware of this until the blind was broken. Those who received 5 sham sessions initially were offered the opportunity to receive 5 further active sessions.

Study	*N* [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
Brunoni et al. (2011b)	31	MDD and BP	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	35	20 mins, 10 sessions (2 per day for 5 consecutive days)	HRSD, BDI	Improvement in depressive symptoms post-tDCS, maintained for at least 1 month. Depression severity was positively related with symptom improvement.	
Martin et al. (2011)	11	MDD and BP	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right upper arm	2	35 (100 for extracephalic electrode)	20 mins, 20 sessions (1 per weekday for 4 consecutive weeks)	MADRS, IDS, CGI-S, QIDS-SR, MADRS-SR	Improvement in depressive symptoms post-tDCS.	Participants were non-responders or relapsers from Loo et al. (2012).

Study	*N* [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
Blumberger et al. (2012)	24	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right DLPFC	2	35	20 mins, 15 sessions (1 per weekday for 3 consecutive weeks)	HRSD, MADRS, BPRS, BDI-II	No improvement in depressive symptoms after active versus sham tDCS.	
Dell'Osso et al. (2012)	23	MDD and BP	Open-label, blind-rater, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	32	20 mins, 10 sessions (2 per day for 5 consecutive days)	MADRS, HRSD	Improvement in depressive symptoms post-tDCS, maintained for at least 1 week.	
Knotkova et al. (2012)	8	MDD (co-diagnosed HIV)	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right supraorbital area	2	25	20 mins, 10 sessions (1 per weekday for 2 consecutive weeks)	HRSD, MADRS	Improvement in depressive symptoms post-tDCS, maintained for at least 2 weeks (further improvement in MADRS scores only).	No mention of DSM/ICD diagnosis.

Study	*N* [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
Loo et al. (2012) *[Phase I]*	58	MDD and BP	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right lateral orbit	2	35	20 mins, 15 sessions (1 per weekday for 3 consecutive weeks)	MADRS, IDS, CGI-S, QIDS-C, QIDS-SR	Improvement in depressive symptoms (MADRS scores only) after active versus sham tDCS, but an equal number of participants in each group met the criterion for response and no participants met the criterion for remission.	

Study	*N* [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
Loo et al. (2012) *[Phase II]*	52	MDD and BP	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right lateral orbit	2	35	20 mins, 15 sessions (1 per weekday for 3 consecutive weeks) then additional weekly sessions for 1-month (responders only)	MADRS, IDS, CGI-S, QIDS-C, QIDS-SR	27 participants met the criterion for response post-tDCS. There were 22 and 20 responders at 1-week and 1-month follow-ups, respectively.	Participants previously received active or sham tDCS in phase I of the trial (Loo et al., 2012). The group who received active tDCS in phase I had better responder rates after phase II.
Palm et al. (2012)	22	MDD and BP	Randomised, double-blind, sham-controlled, crossover	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supraorbital area	1 or 2	35	20 mins, 10 sessions (1 per weekday for 2 consecutive weeks)	HRSD, PANAS, BDI	No improvement in clinical depression ratings, but increase in subjectively reported positive emotions (PANAS), after active versus sham tDCS.	

Study	*N* [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
Alonzo, Chan, Martin, Mitchell, and Loo (2013)	64	MDD and BP	Exploratory analysis of Loo et al. (2012)		No tDCS performed					MADRS	Improvement in dysphoria and retardation after active versus sham tDCS.	Used Loo et al. (2012) dataset.
Brunoni et al. (2013a)	82	MDD and BP (BP-II and BP-NOS only)	Open-label, blind-rater, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	35	20 mins, 10 sessions (2 per day for 5 consecutive days)	HRSD, BDI	Improvement in depressive symptoms post-tDCS. Use of benzodiazepines was associated with a worse outcome.	

Study	*N* [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
Brunoni et al. (2013b) *[Phase I SELECT-TDCS]*	103	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS + placebo pill; (ii) sham tDCS + sertraline; (iii) tDCS + sertraline; (iv) sham tDCS + placebo pill	Left DLPFC	Right DLPFC	2	25	30 mins, 12 sessions (1 per weekday for 2 consecutive weeks then 1 per week for 2 alternate weeks)	MADRS, HRSD, CGI-S, BDI	Improvement in depressive symptoms after active versus sham tDCS. Greatest effects after combined tDCS/sertraline treatment, maintained for at least 2 weeks.	

Study	*N* [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
D'Urso et al. (2013)	1	MDD	Open-label, uncontrolled	(i) tDCS; (ii) tDCS + CBT	Left DLPFC	Right DLPFC	1.5	-	10 sessions (1 per weekday for 2 consecutive weeks) x 2	HRSD	Improvement in depressive symptoms post-tDCS, only partially maintained over the 4-week follow-up period. The combined treatment induced acute improvements and complete remission of symptoms at 12-month follow-up.	CBT sessions were performed weekly during tDCS treatment and throughout the following 6 months.

Study	*N* [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
Martin et al. (2013)	26	MDD and BP	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right lateral orbit or right upper arm	2	35 (100 for extracephalic electrode)	20 mins (1 per week for 3 consecutive months then 1 per fortnight for 3 consecutive months)	MADRS, relapse rates	After tDCS, half the sample survived for at least 24 weeks without relapse.	Participants were from Loo et al. (2012) or Martin et al. (2011). Three participants commenced a new antidepressant treatment during the study.
Valiengo et al. (2013) *[Phase II SELECT-TDCS]*	23	MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	25	30 mins, 10 sessions (1 per weekday for 2 consecutive weeks)	MADRS	Improvement in depressive symptoms post-tDCS.	Participants were non-responders who received sham tDCS in phase I of SELECT-TDCS (Brunoni et al., 2013b).

Study	*N* [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
Valiengo et al. (2013) *[Phase III SELECT-TDCS]*	42	MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	25	30 mins, 9 sessions (1 per week for 6 alternative weeks then 1 per month for 3 consecutive months)	MADRS relapse rates	After tDCS, half the sample survived for at least 24 weeks without relapse. The mean response duration was 11.7 weeks.	Participants were responders who received active tDCS in phase I or phase II of SELECT-TDCS (Brunoni et al., 2013b; Valiengo et al., 2013).
Wolkenstein and Plewnia (2013)	22	MDD	Randomised, double-blind, sham-controlled, crossover	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right deltoid	1	35	20 mins, 1 session	PANAS	No change in subjective mood state after active versus sham tDCS.	
Brunoni et al. (2014a)	37	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS + CCT; (ii) sham tDCS + CCT	Left DLPFC	Right DLPFC	2	25	30 mins, 10 sessions (1 per weekday for 2 consecutive weeks)	HRSD, BDI	Both groups showed similar improvement in depressive symptoms after treatment. Active tDCS + CCT was	

Study	*N* [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
											not superior to sham tDCS + CCT.	
Brunoni et al. (2014b)	120	MDD	Exploratory analysis of Brunoni et al. (2013b)		No tDCS performed					MADRS	Improvement in concentration difficulties, pessimistic thoughts, and suicidal thoughts after active versus sham tDCS.	Used Brunoni et al. (2013b) dataset.
Dell'Osso et al. (2014)	23	MDD and BP	Follow-up of Dell'Osso et al. (2012), blind-rater		No tDCS performed					MADRS, HRSD	Improvement in depressive symptoms post-tDCS, maintained for at least 3 months in half the sample.	Participants were from Dell'Osso et al. (2012).

Study	*N* [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
Ho et al. (2014)	14	MDD	Open-label, uncontrolled	(i) Fronto-occipital tDCS; (ii) fronto-cerebellar tDCS	Left supraorbital area	(i) Bilateral occipital lobe; (ii) bilateral cerebellum	2	35 (100/50 for cathodes)	20 mins, 20 sessions (1 per weekday for 4 consecutive weeks)	MADRS	Improvement in depressive symptoms after fronto-occipital tDCS only.	
Player et al. (2014)	18	MDD and BP-II	Double-blind, sham-controlled (*n* = 6); open-label, uncontrolled (*n* = 12)	(i) tDCS; (ii) sham tDCS (*n* = 6)	Left DLPFC	Right frontal area, right upper arm, or occipital-cerebellar region	2-2.5	-	20-30 mins, 13-21 sessions (consecutive weekdays)	MADRS	Improvement in depressive symptoms after sham tDCS, but greater improvement after active tDCS.	Participants were from several different trials which varied in study design/tDCS parameters. Clinical results from one subject were also reported in Loo et al. (2012).

Study	*N* [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
Segrave et al. (2014)	27	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS + CCT; (ii) sham tDCS + CCT; (iii) tDCS + sham CCT	Left DLPFC	Right lateral orbit	2	35	24 mins, 5 sessions (1 per day for 5 consecutive days)	MADRS, BDI-II	Improvement in depressive symptoms post-tDCS, partially maintained for at least 3 weeks (BDI-II scores only). Combined tDCS/CCT treatment was most effective but had a delayed benefit.	
Shiozawa et al. (2014a)	1	MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right deltoid	2	-	30 mins, 10 sessions (1 per weekday for 2 consecutive weeks)	HRSD	Improvement in depressive symptoms post-tDCS, maintained for at least 3 weeks.	No mention of DSM/ICD diagnosis.

Study	*N* [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
Bennabi et al. (2015)	23	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supraorbital area	2	35	30 mins, 10 sessions (2 per day for 5 consecutive days)	HRSD, MADRS, BDI	No improvement in depressive symptoms after active versus sham tDCS, but more participants in the active group met the response and remission criteria immediately, 12 days, and 30 days after treatment.	
Ho et al. (2015)	4	MDD	Open-label, uncontrolled	(i) tDCS	Left fronto-temporal region	Right fronto-temporal region	2.5	35/16	30 mins, 20 sessions (1 per weekday for 4 consecutive weeks)	MADRS	Improvement in depressive symptoms after tDCS. At the end of treatment, two participants met the criteria for response and one met the	Participants had previously received multiple courses of tDCS (Chan et al., 2013; Loo et al., 2012; Martin et al., 2011, and unpublished data).

Study	*N* [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
											criteria for remission.	
Shiozawa et al. (2015)	1	MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	35	20 mins, 5 sessions (1 per day for 5 consecutive days)	HRSD	Intensification of depressive symptoms after tDCS.	No mention of DSM/ICD diagnosis. Patient had right hemispheric dominance (he was left-handed and was diagnosed with dyslexia during childhood).

BDI, Beck Depression Inventory; BDI-II, Beck Depression Inventory-II; BP, bipolar disorder; BP-II, bipolar II disorder; BP-NOS, bipolar disorder not otherwise specified; BPRS, Brief Psychiatric Rating Scale; CCT, cognitive control training; CGI, Clinical Global Impression; CGI-S, Clinical Global Impression - Severity scale; DLPFC, dorsolateral prefrontal cortex; DSM, Diagnostic and Statistical Manual of Mental Disorders; HRSD, Hamilton Rating Scale for Depression; ICD, International Classification of Diseases; IDS, Inventory of Depressive Symptomatology; MADRS, Montgomery–Åsberg Depression Rating Scale; MADRS-SR, Montgomery–Åsberg Depression Rating Scale - Self-Report; MDD, major depressive disorder; PANAS, Positive and Negative Affect Schedule; PGI-I, Patient Global Impression of Improvement; QIDS-C, Quick Inventory of Depressive Symptomatology -

Clinician Rating; QIDS-SR, Quick Inventory of Depressive Symptomatology - Self-Report; SELECT-TDCS, The sertraline versus electrical current therapy for treating depression clinical study; tDCS, transcranial direct current stimulation; VAS, visual analogue scale.

[a] *N* refers to the number of participants whose data was included at the final stage of analysis.

2.4.3.2 Schizophrenia

Studies examining the clinical effects of tDCS in schizophrenia have mostly employed an electrode montage in which the anode is placed over the l-DLPFC and the cathode is positioned over the left temporoparietal junction (l-TPJ). This set-up appears to have been consistently successful in ameliorating symptoms of the illness; for example, Brunelin et al. (2012a) demonstrated that in 30 patients, 10 sessions of twice-daily sham-controlled tDCS robustly reduced auditory verbal hallucinations (AVHs; indexed by the Auditory Hallucination Rating Scale [AHRS]) acutely and at 3-month follow-up. Improvements in other schizophrenic symptoms, according to the total Positive and Negative Syndrome Scale (PANSS) score, were also recorded (Brunelin et al., 2012a). Mondino, Haesebaert, Poulet, Suaud-Chagny, and Brunelin (2015c) administered the same treatment protocol to a group of 28 patients, 15 of whom had previously taken part in the aforementioned study (Brunelin et al., 2012a), and also observed a large decrease in treatment-resistant AVH frequency in the active versus sham tDCS group.

Additional evidence of efficacy for this tDCS montage and protocol (10 twice-daily sessions, anode l-DLPFC/cathode l-TPJ) comes from three further open-label trials in which a total of 60 schizophrenic patients with persistent auditory hallucinations (AHs) presented significant reductions in Psychotic Symptoms Rating Scales (PSYRATS)/AHRS scores following treatment (Bose et al., 2014; Brunelin, Hasan, Haesebaert, Nitsche, & Poulet, 2015; Shivakumar et al., 2015). While all participants experienced improvements, being a non-smoker (Brunelin et al., 2015) and carrying a particular variant of a neuroplasticity-related gene (catechol-O-methyltransferase [*COMT*]) (Shivakumar et al., 2015) were both associated with having a greater therapeutic response. A number of case reports/series describing patients with refractory schizophrenia have also offered support (Brunelin et al., 2012b; Jacks, Kalivas,

Mittendorf, Kindt, & Short, 2014; Narayanaswamy et al., 2014; Nawani et al., 2014a; Nawani et al., 2014b; Rakesh et al., 2013; Shenoy et al., 2015; Shivakumar et al., 2014). For instance, Shenoy et al. (2015) recorded near-total improvement of the exacerbation of AVHs during pregnancy, Narayanaswamy et al. (2014) noted a delayed but persistent improvement in negative symptoms, and Rakesh et al. (2013) observed complete cessation of AVHs immediately after the first two tDCS sessions and at post-intervention re-assessment. Shivakumar et al. (2014) also witnessed a tDCS-induced termination of AVHs, and subsequently found that application of intermittent booster tDCS (6 sessions) resulted in sustained improvements for a period of one year.

Less positive results were obtained in one case report of a patient presenting with severe, treatment-resistant symptoms who received a higher acute dose of tDCS (20 twice-daily sessions, anode l-DLPFC/cathode l-TPJ) but did not show any clinical gains (Shiozawa et al., 2014d). In addition, although Praharaj, Behere, and Sharma (2015) did observe a reduction of AHs in a patient with treatment-resistant schizophrenia following 10 sessions of tDCS, PSYRATS scores returned to baseline levels six days later. Interestingly, Bose et al. (2015) documented a lack of clinical response to 18 twice-daily sessions of anode l-DLPFC/cathode l-TPJ tDCS in a patient with treatment resistant AVHs; however, significant improvements in symptoms (indexed by the PSYRATS) were subsequently recorded after an additional 20 sessions in which the electrodes were placed at homologous sites on the right side of the brain.

Shiozawa, da Silva, Cordeiro, Fregni, and Brunoni (2013b) conducted a case study of tDCS in patients with long-term, refractory schizophrenia, opting for a unique protocol targeted at the selective improvement of visual hallucinations (VHs) and AHs. Twenty sessions of tDCS were performed in two blocks with a 5-day interval between: for the

first 10 sessions, the cathode was placed over the occipital area (to hypothetically inhibit VHs) and for the remaining 10 sessions over the l-TPJ (to hypothetically inhibit AHs) (Shiozawa et al., 2013b). The anode was positioned over the l-DLPFC throughout (Shiozawa et al., 2013b). Although a transitory increase in hallucinations was observed during the period of stimulation, this was followed by a reduction in VHs and AHs (assessed with the Launay Slade Hallucination Scale [LSHS] and the AHRS, respectively), as well as marked improvements in other positive, negative, and general symptoms (indexed by the PANSS) (Shiozawa et al., 2013b).

A number of other electrode montages have also been trialled for the treatment of schizophrenia, and findings have been mixed. For example, Palm et al. (2013) observed considerable improvement in positive and negative symptoms (using several clinical assessment tools) following a 2-week course of anodal tDCS to the l-DLPFC (the cathode was placed over the right supraorbital area) in a patient with refractory schizophrenia. In contrast, 29 patients who received 5 sessions of sham-controlled tDCS at the same parameters experienced no clinical benefits (indexed by the PANSS and the PSYRATS) (Smith et al., 2015). Shiozawa, da Silva, Cordeiro, Fregni, and Brunoni (2013a) described a treatment-resistant patient who achieved complete remission from catatonic symptoms (indexed by the Bush–Francis catatonic scale) in response to 10 sessions of tDCS over the bilateral DLPFC (anodal left/cathodal right). Gomes et al. (2015) later replicated this protocol in an RCT of 15 participants and correspondingly found a reduction in negative symptoms (according to the PANSS) after active versus sham tDCS. Although no effects were reported for positive symptoms, the real tDCS group had higher scores on the positive subscale of the PANSS at baseline. An improvement in negative but not positive symptoms was also demonstrated by 9 further patients following 10 sessions of anodal l-DLPFC tDCS (with the cathode placed

extracephalically) (Kurimori, Shiozawa, Bikson, Aboseria, & Cordeiro, 2015). Finally, Homan et al. (2011) showed that 10 sessions of cathodal stimulation over Wernicke's area (the anode was positioned over the right supraorbital area) led to persisting reductions in AVHs and other symptoms (indexed by the Hallucination Change Scale, PANSS, and the PSYRATS) in a patient with treatment-resistant schizophrenia.

Table 2.3 Studies in patients with schizophrenia (in chronological order).

Study	*N* [a]	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
		Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm²)	Duration, number, and frequency			
Homan et al. (2011)	1	Open-label, uncontrolled	(i) tDCS	Right supraorbital area	Wernicke's area	1	35	15 mins, 10 sessions (1 per day for 10 consecutive days)	HCS, PANSS, PSYRATS	Reduction in AVH and improvement in other schizophrenic symptoms post-tDCS, maintained for at least 6 weeks.	No mention of DSM/ICD diagnosis.
Brunelin et al. (2012b)	2	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	-	20 mins, 10 sessions (2 per day for 5 consecutive days)	PANSS, AHRS	Reduction in AH and improvement in other schizophrenic symptoms post-tDCS, maintained for at least 3 months.	
Brunelin et al. (2012a)	30	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Left TPJ	2	35	20 mins, 10 sessions (2 per day for 5 consecutive days)	AHRS, PANSS	Reduction in AVH (maintained for at least 3 months) and improvement in other schizophrenic symptoms after active versus sham tDCS.	

Study	*N* [a]	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
		Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm²)	Duration, number, and frequency			
Palm et al. (2013)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right supraorbital area	2	-	20 mins, 10 sessions (1 per weekday for 2 consecutive weeks)	PANSS, SANS, CDSS	Improvement in positive and negative schizophrenic symptoms post-tDCS.	
Rakesh et al. (2013)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	35	20 mins, 10 sessions (2 per day for 5 consecutive days)	AHRS	Complete cessation of AVH post-tDCS.	
Shiozawa et al. (2013b)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Occipital area then TPJ	2	-	20 mins, 20 sessions (1 per day for 10 consecutive days, 5 day break, then 1 per day for 10 consecutive days)	PANSS, LHS, AHRS	Transitory increase during tDCS, followed by reduction post-tDCS, in AH and VH, maintained for at least 2 months, and improvement in other schizophrenic symptoms after tDCS.	No mention of DSM/ICD diagnosis.

Study	*N* [a]	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
		Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm²)	Duration, number, and frequency			
Shiozawa et al. (2013a)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	35	20 mins, 10 sessions (1 per day for 10 consecutive days)	BFCRS	Improvement in catatonic symptoms during tDCS treatment course. Patient was asymptomatic at 4-month follow-up.	No mention of DSM/ICD diagnosis.
Bose et al. (2014)	21	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	35	20 mins, 10 sessions (2 per day for 5 consecutive days)	PSYRATS (AHS)	Reduction in AH post-tDCS.	
Jacks et al. (2014)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	-	20 mins, 10 sessions (2 per day for 5 consecutive days)	PANSS	Improvement in delusions, AH, blunted affect, emotional withdrawal, and general psychopathology PANSS score post-tDCS, but no change in positive or negative	Participant received an acute course of ECT plus weekly maintenance sessions for several months prior to commencement of tDCS.

Study	*N* [a]	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
		Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm²)	Duration, number, and frequency			
										PANSS subscale scores.	
Narayanaswamy et al. (2014)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	-	20 mins, 10 sessions (2 per day for 5 consecutive days)	AHRS, SANS	Delayed improvement in negative symptoms and small reduction in AVH, maintained for at least 6 months.	
Nawani et al. (2014a)	5	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	-	20 mins, 10 sessions (2 per day for 5 consecutive days)	AHRS	Reduction in AVH post-tDCS.	
Nawani et al. (2014b)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	-	20 mins, 10 sessions (2 per day for 5 consecutive days)	AHRS	Reduction in AVH post-tDCS.	

Study	*N* [a]	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
		Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm²)	Duration, number, and frequency			
Shiozawa et al. (2014d)	1	Open-label, uncontrolled	(i) tDCS	Left TPJ	Right TPJ	2	35	20 mins, 10 sessions (1 per day for 10 consecutive days)	PANSS	No improvement in schizophrenic symptoms post-tDCS.	No mention of DSM/ICD diagnosis.
Shivakumar et al. (2014)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	-	20 mins, 10 sessions (2 per day for 5 consecutive days) plus 6 intermittent booster sessions over 1 year (2 per day, single day)	PSYRATS (AHS)	Complete cessation of AVH after acute course of tDCS, maintained for 3 months. Booster tDCS sessions controlled 3 subsequent relapses over 1 year. Participant was free of AVH at 1-year follow-up.	

Study	*N* [a]	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
		Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm²)	Duration, number, and frequency			
Bose et al. (2015)	1	Open-label, uncontrolled	(i) left-sided tDCS; (ii) right-sided tDCS	(i) Left DLPFC; (ii) right DLPFC	(i) Left TPJ; (ii) right TPJ	2	35	(i) 20 mins, 18 sessions (2 per day for 9 consecutive days); (ii) 20 mins, 20 sessions (2 per day for 10 consecutive days)	PSYRATS (AHS)	No improvement in schizophrenic symptoms after left-sided tDCS, but reduction in AH after right-sided tDCS.	Electrode positioning was modified due to lack of clinical response.
Brunelin et al. (2015)	16	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	35	20 mins, 10 sessions (frequency not stated)	AHRS	Reduction in AH post-tDCS.	Patients with a comorbid tobacco use disorder (n = 10) were less responsive to tDCS.
Gomes et al. (2015)	15	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right DLPFC	2	-	20 mins, 10 sessions (1 per weekday for 2 consecutive weeks)	PANSS	Improvement in negative but not positive symptoms after active versus sham tDCS.	At baseline, the tDCS group had higher PANSS scores for the positive scale relative to the sham tDCS group.

Study	*N* [a]	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
		Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm²)	Duration, number, and frequency			
Kurimori et al. (2015)	9	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right deltoid	2	-	20 mins, 10 sessions (1 per weekday for 2 consecutive weeks)	PANSS	Improvement in negative but not positive symptoms post-tDCS.	No mention of DSM/ICD diagnosis.
Mondino et al. (2015c)	28	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Left TPJ	2	35	20 mins, 10 sessions (2 per day for 5 consecutive days)	AVH frequency	Reduction in AVH after active versus sham tDCS.	No mention of DSM/ICD diagnosis. 15 participants were from Brunelin et al. (2012a). AVH frequency method of assessment not stated.
Praharaj et al. (2015)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	25	20 mins, 5 sessions (1 per day for 5 consecutive days)	PSYRATS (AHS)	Reduction in AH post-tDCS, but symptoms returned to baseline levels 6 days after treatment.	No mention of DSM/ICD diagnosis.

Study	*N* [a]	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
		Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm²)	Duration, number, and frequency			
Shenoy et al. (2015)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	-	20 mins, 10 sessions (2 per day for 5 consecutive days)	AHRS	Reduction in AVH post-tDCS, with further improvement for at least 1 month.	Participant was pregnant, and received tDCS treatment previously (reference given to conference abstract only).
Shivakumar et al. (2015)	23	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	35	20 mins, 10 sessions (2 per day for 5 consecutive days)	PSYRATS (AHS)	Reduction in AH post-tDCS.	Allelic variations in the COMT gene influenced the clinical efficacy of tDCS.
Smith et al. (2015)	29	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supraorbital area	2	5.08	20 mins, 5 sessions (1 per day for 5 consecutive days in most cases)	PANSS, PSYRATS	No improvement in schizophrenic symptoms after active versus sham tDCS.	

AH, auditory hallucinations; AHRS, Auditory Hallucination Rating Scale; AHS, Auditory Hallucinations Subscale; AVH, auditory verbal hallucinations; BFCRS, Bush-Francis Catatonia Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; COMT, Catechol-O-methyltransferase; DLPFC, dorsolateral prefrontal cortex; DSM, Diagnostic and

Statistical Manual of Mental Disorders; ECT, electroconvulsive therapy; HCS, Hallucination Change Scale; ICD, International Classification of Diseases; LHS, Launay Slade Hallucination Scale; PANSS, Positive And Negative Syndrome Scale; PSYRATS, Psychotic Symptom Rating Scales; SANS, Scale for the Assessment of Negative Symptoms; tDCS, transcranial direct current stimulation; TPJ, temporo-parietal junction; VH, visual hallucinations.

[a] *N* refers to the number of participants whose data was included at the final stage of analysis.

2.4.3.3 Substance use disorders

The literature on the clinical utility of tDCS for treating SUDs consists of a small number of RCTs which have generated mixed results. Boggio et al. (2008b) were the first to publish data here: in a group of 13 participants with alcohol dependence, one session of tDCS to the bilateral DLPFC (either anodal left/cathodal right or anodal right/cathodal left) was shown to decrease alcohol craving (indexed by the Alcohol Urge Questionnaire [AUQ]) relative to sham stimulation. Interestingly, Klauss et al. (2014) found that a higher dose of bilateral DLPFC tDCS (10 twice-daily sessions) did not diminish craving (assessed with the Obsessive Compulsive Drinking Scale [OCDS]) but reduced relapse probability in 33 alcohol dependent individuals (Klauss et al., 2014). A dissociation between levels of craving and the likelihood of relapse to alcohol use was also reported by da Silva et al. (2013): 13 alcoholics received 5 weekly sessions of sham-controlled unilateral DLPFC stimulation (anode over the l-DLPFC, cathode over the right supradeltoid area) and, although the treatment suppressed cravings (indexed by the OCDS), there was an unexpected trend for more relapses in the active versus sham tDCS group. The same electrode montage was adopted in a single-session trial involving 49 alcohol-dependent patients in which no anti-craving effects were observed (Nakamura-Palacios et al., 2012).

Three studies examining the therapeutic potential of tDCS in individuals addicted to substances other than alcohol have been conducted. In the first, Shahbabaie et al. (2014) provided evidence suggesting that tDCS has a state-dependent effect on craving in methamphetamine (mAMP) users. Thirty patients underwent one session of sham-controlled anodal tDCS over the right DLPFC (r-DLPFC) (the cathode was placed over the left supraorbital area) and, while active tDCS acutely reduced craving at rest, it increased craving during mAMP-related cue exposure. In the second, Conti, Moscon,

Fregni, Nitsche, and Nakamura-Palacios (2014) administered 5 sessions of real or sham bilateral DLPFC stimulation (anodal right/cathode left) to 13 crack-cocaine addicted individuals and observed a higher percentage of abstinence at 3-month follow-up in those assigned to the real tDCS group. This study was later replicated using a larger group of patients (n = 36), whose crack-cocaine cravings were suppressed for at least one week by active versus sham tDCS (Batista, Klauss, Fregni, Nitsche, & Nakamura-Palacios, 2015).

Table 2.4 Studies in patients with substance use disorders.

Study	*N* [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
Boggio et al. (2008b)	13	Alcohol dependence	Randomised, double-blind, sham-controlled, crossover	(i) anode left/cathode right tDCS; (ii) anode right/cathode left tDCS; (iii) sham tDCS	(i) Left DLPFC, (ii) Right DLPFC	(i) Right DLPFC, (ii) Left DLPFC	2	35	20 mins, 1 session	AUQ	Reduction in alcohol craving after anode left/cathode right tDCS and anode right/cathode left tDCS versus sham tDCS. Alcohol craving could not be increased by alcohol cues after active versus sham tDCS.	
Nakamura-Palacios et al. (2012)	49	Alcohol dependence	Randomised, single-blind, sham-controlled, crossover	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supradeltoid area	1	35	10 mins, 1 session	OCDS	No reduction in alcohol craving after active versus sham tDCS.	Alcohol craving was not provoked with cues.

Study	N [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm²)	Duration, number, and frequency			
da Silva et al. (2013)	13	Alcohol dependence	Randomised, single-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supradeltoid area	2	35	20 mins, 5 sessions (1 per week for 5 consecutive weeks)	OCDS, verbally assessed relapse rates	Reduction in alcohol craving after active versus sham tDCS, but trend for relapse during treatment in active tDCS group.	
Klauss et al. (2014)	33	Alcohol dependence	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Right DLPFC	Left DLPFC	2	35	13 mins, 10 sessions (2 per day, with a 20 min interval, for 5 consecutive days)	Verbally assessed relapse rates, OCDS	No reduction in alcohol craving after active versus sham tDCS, but patients in the active tDCS group were more likely to survive for at least 6 months without relapse.	Alcohol craving was not provoked with cues.
Shahbabaie et al. (2014)	30	mAMP dependence	Randomised, double-blind, sham-controlled, crossover	(i) tDCS; (ii) sham tDCS	Right DLPFC	Left supraorbital area	2	35	20 mins, 1 session	Self-reported mAMP craving (VAS), CICT	Reduction in mAMP craving at rest, but increase in cue-induced craving, during active versus sham tDCS.	Effects of tDCS were state-dependent.

Study	N [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm²)	Duration, number, and frequency			
Conti et al. (2014)	13	Crack-cocaine dependence	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Right DLPFC	Left DLPFC	2	35	20 mins, 5 sessions (1 per day for 5 alternate days)	Relapses/ periods of abstinence	No between-group differences in relapse rates during the treatment period. At 3-month follow-up, more participants in the real than in the sham tDCS group maintained abstinence from crack-cocaine.	Only 50% of participants in the sham group completed all treatment sessions (compared to 86% in the real group).
Batista et al. (2015)	36	Crack-cocaine dependence	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Right DLPFC	Left DLPFC	2	35	20 mins, 5 sessions (1 per day for 5 alternate days)	Crack-cocaine craving (scale composed of 5 items from the OCDS)	Reduction in crack-cocaine craving after active versus sham tDCS, maintained for at least 1 week.	

AUQ, Alcohol Urge Questionnaire; CICT, Computerised Cue-Induced Craving Assessment Task; DLPFC, dorsolateral prefrontal cortex; mAMP, methamphetamine; OCDS, Obsessive Compulsive Drinking Scale; tDCS, transcranial direct current stimulation; VAS, visual analogue scale.

[a] *N* refers to the number of participants whose data was included at the final stage of analysis.

2.4.3.4 Other psychiatric disorders

Limited data exist on the clinical efficacy of tDCS in other psychiatric disorders; however, some promising results have been reported. For example, Shiozawa et al. (2014c) described the case of a patient with treatment-resistant GAD who underwent a three-week course of cathodal r-DLPFC tDCS (the anode was placed over the left deltoid) and was asymptomatic both acutely and at one-month follow-up. Additionally, Khedr, Elfetoh, Ali, and Noamany (2014) showed that 10 sessions of anodal stimulation over the l-DLPFC (the cathode was positioned over the right arm) relieved eating disorder symptoms in 5 of 7 AN patients and, furthermore, 4 participants maintained these improvements for at least 1 month after the end of treatment.

Mondino, Haesebaert, Poulet, Saoud, and Brunelin (2015b) demonstrated that 10 sessions of twice-daily cathodal tDCS over the left OFC (the anode was positioned over the right occipital cortex) induced delayed but lasting reductions in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores in a patient with treatment-resistant OCD. Sustained symptom improvements were also recorded in two patients with drug-resistant OCD, following 20 sessions of twice-daily anodal tDCS over the left pre-SMA/SMA (the cathode was placed over the right supraorbital area) (Narayanaswamy et al., 2015). Interestingly, D'Urso et al. (2015) found that a two-week course of anodal tDCS over the same region (with the cathode placed extracephalically) exacerbated a patient's OCD symptoms. The electrodes were then inverted for a further 10 sessions, which reduced Y-BOC scores (beyond baseline levels) for at least 3 months post-treatment (D'Urso et al., 2015). Lastly, Volpato et al. (2013) administered 10 sessions of cathodal l-DLPFC tDCS (with the anode placed over the posterior neck base) to a patient with severe and enduring OCD and, although the intervention had no effect on OCD-specific symptoms (indexed by the Y-BOCS), it improved the patient's comorbid

anxiety and depression (assessed with the Hamilton Rating Scale for Anxiety [HRSA] and the HRSD, respectively).

Table 2.5 Studies of patients with other psychiatric disorders (obsessive compulsive disorder, generalised anxiety disorder, and anorexia nervosa).

Study	*N* [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm²)	Duration, number, and frequency			
Volpato et al. (2013)	1	OCD (comorbid MDD and GAD)	Double-blind, sham-controlled	(i) tDCS; (ii) sham tDCS; (iii) rTMS; (iv) sham rTMS	Posterior neck base	Left DLPFC	2	35	20 mins, 10 sessions (1 per weekday for 2 consecutive weeks)	Y-BOCS, HRSD, HRSA	No improvement in OCD symptoms, but improvement in depression and anxiety, after real versus sham tDCS.	
Shiozawa et al. (2014c)	1	GAD	Open-label, uncontrolled	(i) tDCS	Left deltoid	Right DLPFC	2	25	30 mins, 15 sessions (1 per weekday for 3 consecutive weeks)	GAD-7, BAI, HRSA	Improvement in anxiety symptoms during tDCS treatment course. Patient was asymptomatic post-tDCS and at 1-month follow-up.	No mention of DSM/ICD diagnosis.

Study	N [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm²)	Duration, number, and frequency			
Khedr et al. (2014)	7	AN	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right arm	2	24 (100 for extracephalic electrode)	25 mins, 10 sessions (1 per weekday for 2 consecutive weeks)	EAT, EDI	Improvement in eating disorder symptoms post-tDCS, maintained for at least 1 month. Large variability in responses.	
D'Urso et al. (2015)	1	OCD	Open-label, uncontrolled	(i) anodal tDCS; (ii) cathodal tDCS	(i) pre-SMA; (ii) right deltoid	(i) Right deltoid; (ii) pre-SMA	2	25	20 mins, 20 sessions (1 per weekday for 4 consecutive weeks)	Y-BOCS	Worsening and improvement of OCD symptoms after anodal and cathodal tDCS, respectively. Overall reduction in symptoms at the end of treatment, maintained for at least 3 months.	The polarity of the electrodes was inverted after 10 sessions due to exacerbation of symptoms.

Study	N [a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm²)	Duration, number, and frequency			
Mondino et al. (2015b)	1	OCD	Open-label, uncontrolled	(i) tDCS	Right occipital cortex	Left OFC	2	35 (100 for anode)	20 mins, 10 sessions (2 per day for 5 consecutive days)	Y-BOCS	Delayed improvement in OCD symptoms, maintained for at least 1 month.	
Narayanaswamy et al. (2015)	2	OCD	Open-label, uncontrolled	(i) tDCS	Left pre-SMA/SMA	Right supraorbital area	2	35	20 mins, 20 sessions (2 per day for 10 consecutive days)	Y-BOCS	Improvement in OCD symptoms post-tDCS, maintained for at least 1 month/2 months.	

AN, anorexia nervosa; BAI, Beck Anxiety Inventory; DLPFC, dorsolateral prefrontal cortex; DSM, Diagnostic and Statistical Manual of Mental Disorders; EAT, Eating Attitudes Test; EDI, Eating Disorder Inventory; GAD, generalised anxiety disorder; GAD-7, Generalised Anxiety Disorder 7-item scale; HRSA, Hamilton Rating Scale for Anxiety; HRSD, Hamilton Rating Scale for Depression; ICD, International Classification of Diseases; MDD, major depressive disorder; OCD, obsessive compulsive disorder; OFC, orbitofrontal cortex; rTMS, repetitive transcranial magnetic stimulation; SMA, supplementary motor area; tDCS, transcranial direct current stimulation; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

[a] *N* refers to the number of participants whose data was included at the final stage of analysis.

2.5 DISCUSSION

2.5.1 Clinical efficacy

This review provides evidence that tDCS has the potential to ameliorate symptoms associated with several major psychiatric disorders. Most notably, data from a number of RCTs suggest that tDCS interventions comprised of multiple sessions can induce enduring therapeutic effects in patients with depressive disorders and schizophrenia. Further indication of clinical utility in these conditions has come from numerous open-label trials and case reports, often involving patients who have experienced dramatic improvements and, in some instances, achieved full remission following treatment with tDCS. Although research in other mental disorders is somewhat limited, several RCTs support the prospective application of tDCS in SUDs, and emerging data from a small number of patients indicate that tDCS can induce significant clinical gains in people with OCD, GAD, and AN.

Despite evidence that tDCS offers exciting possibilities for treatment development in psychiatry, symptom improvements have been modest or absent in a considerable number of studies. Furthermore, a small number of publications have reported a tDCS-induced exacerbation of symptoms. Multiple factors are likely to contribute to the variability of response in tDCS studies, and these are discussed in turn below.

2.5.1.1 Patient characteristics

A number of inter- and intra-individual biological, psychological, and lifestyle factors appear to influence the clinical efficacy of tDCS. First, differences in genotype have been linked to altered tDCS responding, possibly via impact on anatomical and neurophysiological states. Shivakumar et al. (2015), for example, showed that a

polymorphism at the neuroplasticity-related *COMT* gene moderated the therapeutic effects of tDCS in a group of patients with schizophrenia. Second, the psychological state of participants at the time of stimulation seems to play a role: in SUD, prefrontal tDCS has been found to intensify cravings if those receiving it are in the presence of drug-related cues (Shahbabaie et al., 2014). Third, nicotine smoking has been associated with reduced clinically efficacy of tDCS in patients with schizophrenia (Brunelin et al., 2015). This may explain the negative results reported by Smith et al. (2015), since all participants in this study were regular smokers. Fourth, illness severity has been identified as a predictor of response to tDCS: Ferrucci et al. (2009a) observed a greater therapeutic effect for severe MDD than for mild/moderate MDD.

It has been proposed that degree of treatment-resistance may also influence clinical outcomes of tDCS (Brunoni & Fregni, 2011; Mondino et al., 2014), although this factor has not been explicitly investigated and studies of patients with treatment-resistant disorders have produced both negative (e.g., Bennabi et al., 2015; Blumberger et al., 2012; Palm et al., 2012) and positive (e.g., Dell'Osso et al., 2012; Ferrucci et al., 2009b; Palm et al., 2013) results. Nevertheless, close attention must be paid to the definition of treatment-resistance because, in some instances, studies with negative results (Blumberger et al., 2012; Palm et al., 2012) have used more stringent refractoriness criteria than those with positive ones (Dell'Osso et al., 2012).

2.5.1.2 Concomitant therapy

The medication status of patients varied significantly both within and between studies included in this review. In some cases, tDCS was administered as an "add-on" therapy to a stable dose of medication (e.g., Bose et al., 2014), while other studies excluded participants taking any neuropsychotropic drugs (e.g., Boggio et al., 2008b), included a

mix of medicated and non-medicated patients (e.g., Loo et al., 2010), or failed to address concomitant pharmacotherapy at all (e.g., da Silva et al., 2013). Evidence indicates that particular psychoactive substances can interact with the effects of tDCS; specifically, benzodiazepines have been reported to hinder therapeutic effects, whereas antidepressants have been associated with enhanced outcomes (Brunoni et al., 2013a; Brunoni et al., 2013b). Crucially, three studies which found tDCS to be clinically ineffective permitted benzodiazepine use during the trial (26-33% of patients were taking benzodiazepines) (Bennabi et al., 2015; Blumberger et al., 2012; Brunoni et al., 2014a), and one study which found tDCS to be effective tolerated antidepressant but not benzodiazepine use (52% of patients were taking antidepressants) (Segrave et al., 2014). Nonetheless, Boggio et al. (2008a) used opposing eligibility criteria – allowing benzodiazepine but not antidepressant use – and still observed positive effects. Cognitive-based therapies can also influence clinical outcomes from tDCS (D'Urso et al., 2013; Segrave et al., 2014); however, information regarding the use of concurrent non-pharmacological treatments was seldom provided.

2.5.1.3 Parameters of stimulation

tDCS interventions varied extensively between the reviewed studies according to a range of parameters, such as electrode size and positioning, current amplitude, duration of stimulation, and number and frequency of sessions (see Tables 2.2-2.5). Considerable heterogeneity was even present among studies attempting to treat the same psychiatric disorder. Unsurprisingly, results from several investigations suggested that the number of sessions administered, the placement of the reference electrode, and the anode/cathode polarity moderate the therapeutic effects of tDCS (Bose et al., 2015; D'Urso et al., 2015; Loo et al., 2012; Loo et al., 2010; Martin et al., 2011). Most notably, D'Urso et al. (2015) demonstrated that 10 sessions of anodal tDCS applied to

the pre-SMA led to an exacerbation of symptoms in a patient with OCD; however, when the polarity of the electrodes was inverted (for a further 10 sessions of tDCS), significant and persisting improvements beyond baseline levels were observed.

2.5.1.4 Study design

This review incorporated studies of varying design. Interestingly, the majority of studies with negative results were RCTs (e.g., Blumberger et al., 2012; Klauss et al., 2014; Loo et al., 2012; Nakamura-Palacios et al., 2012; Palm et al., 2012; Smith et al., 2015), which raises the possibility of a placebo effect. Indeed, sham tDCS frequently exerts some degree of influence over outcomes; however, the improvements observed in open-label investigations are unlikely to be the result of placebo mechanisms alone since many of the patients involved in these studies were treatment-resistant, and refractoriness is associated with lower placebo responding (Brunoni, Lopes, Kaptchuk, & Fregni, 2009). It should also be noted that publication bias – in which research with unfavourable results has a lower probability of being published – is more likely to affect open-label, uncontrolled studies than RCTs (Easterbrook, Gopalan, Berlin, & Matthews, 1991). Thus, the higher proportion of RCTs with negative results may be, at least in part, an artefact of such bias.

2.5.2 Safety issues and ethical considerations

Administration of tDCS interventions that comply with recommended safety regulations (current: < 2.5 mA, duration: 20-60 min per session, frequency: ≤ twice per day, application: with electrodes that minimise skin burns) (Fregni et al., 2015) has presented minimal risk across a wide range of participants. Only mild and transient side-effects – such as itching, tingling, and headache – have been reported (Brunoni et al., 2011a), leading to the conclusion that tDCS is a relatively safe procedure. However, the absence

of serious adverse events is not irrefutable evidence that the technique is unequivocally benign, and a number of ethical and safety issues remain (Fitz & Reiner, 2015; Kadosh, Levy, O'Shea, Shea, & Savulescu, 2012; Widdows & Davis, 2014).

Firstly, Brunoni et al. (2011a) argue that adverse events are being neglected in tDCS research, possibly due to a subjective belief that the technique raises negligible safety concerns. In their systematic review of 209 tDCS clinical trials, 92 studies did not report the presence and/or absence of adverse effects, which the authors interpret as evidence of selective reporting bias (Brunoni et al., 2011a). Secondly, despite knowledge that stimulation of one particular cortical site can alter activation and connectivity in regions distal to the electrodes, the nature of the functional networks associated with the target brain areas seems to have little influence in the design of tDCS experiments (Wokke, Talsma, & Vissers, 2014). Data suggest that cognitive enhancement mediated by tDCS can occur at the expense of other cognitive functions (Iuculano & Cohen Kadosh, 2013), yet the potential for collateral behavioural impairments arising from the use of tDCS in psychiatric research has been largely overlooked. Our incomplete understanding of the neural bases of mental disorders and the resultant lack of any standardised stimulation guidelines pose risks for the occurrence of unintended and undesirable effects. Thirdly, Widdows and Davis (2014) point out that qualitative differences in anatomy are sometimes seen in people with mental illness compared to healthy controls; for example, patients with eating disorders have shown low levels of subcutaneous adipose tissue around the head and altered cortical folding. These factors are likely to have an impact on the effects of tDCS-induced electrical currents, therefore extra caution ought to be exercised in such patient groups (Widdows & Davis, 2014). Lastly, tDCS has recently garnered considerable ‘neurohype’ in the media as a portable, painless, inexpensive, and safe therapeutic device. This positive portrayal has the

potential to shape the public's risk-benefit perceptions, promote a therapeutic misconception, and have an impact on the uptake of this technology (Dubljević, Saigle, & Racine, 2014). Without some degree of 'neuromodesty' (Morse, 2012), desperate and vulnerable mentally ill patients may overestimate the benefits and underestimate the risks of tDCS.

2.5.3 Conclusions and future directions

Research into the clinical efficacy of tDCS in psychiatric disorders has grown exponentially over the past decade. We have systematically reviewed the literature and have provided an objective and analytical account of its current state. Overall, data from studies appraised in this review suggest that tDCS has the potential to induce clinically relevant behavioural changes in often difficult-to-treat patient populations, and could thus represent a valuable tool for intervention in a range of mental disorders. Nevertheless, the use of tDCS for treating psychiatric disorders is still in its infancy, and further evidence of its efficacy from large-scale, multi-centred RCTs is required if the transition of this therapy from the laboratory to the clinic is to be considered. Indeed, the approval of repetitive transcranial magnetic stimulation (a related non-invasive neuromodulation technique) as a second-line treatment for major depression in several countries was preceded by extensive sham-controlled investigations (Dell'Osso & Altamura, 2014). It is also essential that steps are taken to resolve the discrepancies in clinical findings; for example, sample variability should be controlled and reproducible stimulation parameters should be defined in terms of optimising therapeutic response for different clinical applications. A better understanding of the neural responses to tDCS will accelerate progress here, and is likely to arise through combined tDCS-neuroimaging experiments (Venkatakrishnan & Sandrini, 2012) and computational neurostimulation approaches (de Berker, Bikson, & Bestmann, 2013). Finally, all

investigators conducting research with tDCS should be mindful of the various safety and ethical issues associated with the use of this neuromodulation technique.

2.6 REFERENCES

Alonso, J., Angermeyer, M. C., Bernert, S., Bruffaerts, R., Brugha, T. S., Bryson, H., . . . Vollebergh, W. A. (2004). Disability and quality of life impact of mental disorders in Europe: Results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatrica Scandinavica. Supplementum, 109*(420), 38-46.

Alonzo, A., Chan, G., Martin, D., Mitchell, P. B., & Loo, C. (2013). Transcranial direct current stimulation (tDCS) for depression: Analysis of response using a three-factor structure of the Montgomery-Asberg depression rating scale. *Journal of Affective Disorders, 150*(1), 91-95.

Batista, E. K., Klauss, J., Fregni, F., Nitsche, M. A., & Nakamura-Palacios, E. M. (2015). A randomized placebo-controlled trial of targeted prefrontal cortex modulation with bilateral tDCS in patients with crack-cocaine dependence. *International Journal of Neuropsychopharmacology, 18*(12).

Bennabi, D., Nicolier, M., Monnin, J., Tio, G., Pazart, L., Vandel, P., & Haffen, E. (2015). Pilot study of feasibility of the effect of treatment with tDCS in patients suffering from treatment-resistant depression treated with escitalopram. *Clinical Neurophysiology, 126*(6), 1185-1189.

Berlim, M. T., Van den Eynde, F., & Daskalakis, Z. J. (2013). Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: A systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *Journal of Psychiatric Research, 47*(1), 1-7.

Blumberger, D. M., Tran, L. C., Fitzgerald, P. B., Hoy, K. E., & Daskalakis, Z. J. (2012). A randomized double-blind sham-controlled study of transcranial direct current stimulation for treatment-resistant major depression. *Frontiers in Psychiatry, 3*, 1-8.

Boggio, P. S., Rigonatti, S. P., Ribeiro, R. B., Myczkowski, M. L., Nitsche, M. A., Pascual-Leone, A., & Fregni, F. (2008a). A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. *International Journal of Neuropsychopharmacology, 11*(2), 249-254.

Boggio, P. S., Sultani, N., Fecteau, S., Merabet, L., Mecca, T., Pascual-Leone, A., . . . Fregni, F. (2008b). Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: A double-blind, sham-controlled study. *Drug and Alcohol Dependence, 92*(1-3), 55-60.

Bose, A., Shivakumar, V., Narayanaswamy, J. C., Nawani, H., Subramaniam, A., Agarwal, S. M., . . . Venkatasubramanian, G. (2014). Insight facilitation with add-on tDCS in schizophrenia. *Schizophrenia Research, 156*(1), 63-65.

Bose, A., Sowmya, S., Shenoy, S., Agarwal, S. M., Chhabra, H., Narayanaswamy, J. C., & Venkatasubramanian, G. (2015). Clinical utility of attentional salience in treatment of auditory verbal hallucinations in schizophrenia using transcranial direct current stimulation (tDCS). *Schizophrenia Research, 164*(1-3), 279-280.

Brunelin, J., Hasan, A., Haesebaert, F., Nitsche, M. A., & Poulet, E. (2015). Nicotine smoking prevents the effects of frontotemporal transcranial direct current stimulation (tDCS) in hallucinating patients with schizophrenia. *Brain Stimulation, 8*(6), 1225-1227.

Brunelin, J., Mondino, M., Gassab, L., Haesebaert, F., Gaha, L., Suaud-Chagny, M. F., . . . Poulet, E. (2012a). Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. *The American Journal of Psychiatry, 169*(7), 719-724.

Brunelin, J., Mondino, M., Haesebaert, F., Saoud, M., Suaud-Chagny, M. F., & Poulet, E. (2012b). Efficacy and safety of bifocal tDCS as an interventional treatment for refractory schizophrenia. *Brain Stimulation, 5*(3), 431-432.

Brunoni, A. R., Amadera, J., Berbel, B., Volz, M. S., Rizzerio, B. G., & Fregni, F. (2011a). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *International Journal of Neuropsychopharmacology, 14*(8), 1133-1145.

Brunoni, A. R., Boggio, P. S., De Raedt, R., Bensenor, I. M., Lotufo, P. A., Namur, V., . . . Vanderhasselt, M. A. (2014a). Cognitive control therapy and transcranial direct current stimulation for depression: A randomized, double-blinded, controlled trial. *Journal of Affective Disorders, 162*, 43-49.

Brunoni, A. R., Ferrucci, R., Bortolomasi, M., Scelzo, E., Boggio, P. S., Fregni, F., . . . Priori, A. (2013a). Interactions between transcranial direct current stimulation (tDCS) and pharmacological interventions in the Major Depressive Episode: Findings from a naturalistic study. *European Psychiatry, 28*(6), 356-361.

Brunoni, A. R., Ferrucci, R., Bortolomasi, M., Vergari, M., Tadini, L., Boggio, P. S., . . . Priori, A. (2011b). Transcranial direct current stimulation (tDCS) in unipolar vs. bipolar depressive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 35*(1), 96-101.

Brunoni, A. R., Ferrucci, R., Fregni, F., Boggio, P. S., & Priori, A. (2012a). Transcranial direct current stimulation for the treatment of major depressive disorder: A summary of preclinical, clinical and translational findings. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 39*(1), 9-16.

Brunoni, A. R., & Fregni, F. (2011). Clinical trial design in non-invasive brain stimulation psychiatric research. *International Journal of Methods in Psychiatric Research, 20*(2), e19-e30.

Brunoni, A. R., Junior, R. F., Kemp, A. H., Lotufo, P. A., Bensenor, I. M., & Fregni, F. (2014b). Differential improvement in depressive symptoms for tDCS alone and combined with pharmacotherapy: An exploratory analysis from the Sertraline vs. Electrical Current Therapy for Treating Depression Clinical Study. *International Journal of Neuropsychopharmacology, 17*(1), 53-61.

Brunoni, A. R., Lopes, M., Kaptchuk, T. J., & Fregni, F. (2009). Placebo response of non-pharmacological and pharmacological trials in major depression: A systematic review and meta-analysis. *PLOS ONE, 4*(3).

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., . . . Fregni, F. (2012b). Clinical research with transcranial direct current stimulation (tDCS): Challenges and future directions. *Brain Stimulation, 5*(3), 175-195.

Brunoni, A. R., Valiengo, L., Baccaro, A., Zanao, T. A., de Oliveira, J. F., Goulart, A., . . . Fregni, F. (2013b). The Sertraline vs. Electrical Current Therapy for Treating Depression Clinical Study: Results from a factorial, randomized, controlled trial. *JAMA Psychiatry, 70*(4), 383-391.

Chan, H. N., Alonzo, A., Martin, D. M., Mitchell, P. B., Sachdev, P., & Loo, C. K. (2013). Augmenting transcranial direct current stimulation with (D)-cycloserine for depression: A pilot study. *Journal of ECT, 29*(3), 196-200.

Conti, C. L., Moscon, J. A., Fregni, F., Nitsche, M. A., & Nakamura-Palacios, E. M. (2014). Cognitive related electrophysiological changes induced by non-invasive cortical electrical stimulation in crack-cocaine addiction. *International Journal of Neuropsychopharmacology, 17*(9), 1465-1475.

D'Urso, G., Brunoni, A. R., Anastasia, A., Micillo, M., de Bartolomeis, A., & Mantovani, A. (2015). Polarity-dependent effects of transcranial direct current stimulation in obsessive-compulsive disorder. *Neurocase, 22*(1), 60-64.

D'Urso, G., Mantovani, A., Micillo, M., Priori, A., & Muscettola, G. (2013). Transcranial direct current stimulation and cognitive-behavioral therapy: Evidence of a synergistic effect in treatment-resistant depression. *Brain Stimulation, 6*(3), 465-467.

da Silva, M. C., Conti, C. L., Klauss, J., Alves, L. G., do Nascimento Cavalcante, H. M., Fregni, F., . . . Nakamura-Palacios, E. M. (2013). Behavioral effects of transcranial direct current stimulation (tDCS) induced dorsolateral prefrontal cortex plasticity in alcohol dependence. *Journal of Physiology, Paris, 107*(6), 493-502.

de Berker, A. O., Bikson, M., & Bestmann, S. (2013). Predicting the behavioral impact of transcranial direct current stimulation: Issues and limitations. *Frontiers in Human Neuroscience, 7*, 613.

Dell'Osso, B., Dobrea, C., Arici, C., Benatti, B., Ferrucci, R., Vergari, M., . . . Altamura, A. C. (2014). Augmentative transcranial direct current stimulation (tDCS) in poor responder depressed patients: A follow-up study. *CNS Spectrums, 19*(4), 347-354.

Dell'Osso, B., Zanoni, S., Ferrucci, R., Vergari, M., Castellano, F., D'Urso, N., . . . Altamura, A. C. (2012). Transcranial direct current stimulation for the outpatient treatment of poor-responder depressed patients. *European Psychiatry, 27*(7), 513-517.

Dell'Osso, B., & Altamura, A. C. (2014). Transcranial brain stimulation techniques for major depression: Should we extend TMS lessons to tDCS? *Clinical Practice and Epidemiology in Mental Health, 10*, 92-93.

Dubljević, V., Saigle, V., & Racine, E. (2014). The rising tide of tDCS in the media and academic literature. *Neuron, 82*(4), 731-736.

Easterbrook, P. J., Gopalan, R., Berlin, J. A., & Matthews, D. R. (1991). Publication bias in clinical research. *The Lancet, 337*(8746), 867-872.

Ferrucci, R., Bortolomasi, M., Brunoni, A. R., Vergari, M., Tadini, L., Giacopuzzi, M., & Priori, A. (2009a). Comparative benefits of transcranial direct current stimulation (tDCS) treatment in patients with mild/moderate vs. severe depression. *Clinical Neuropsychiatry, 6*(6), 246-251.

Ferrucci, R., Bortolomasi, M., Vergari, M., Tadini, L., Salvoro, B., Giacopuzzi, M., . . . Priori, A. (2009b). Transcranial direct current stimulation in severe, drug-resistant major depression. *Journal of Affective Disorders, 118*(1-3), 215-219.

Fitz, N. S., & Reiner, P. B. (2015). The challenge of crafting policy for do-it-yourself brain stimulation. *Journal of Medical Ethics, 41*(5), 410-412.

Frangou, S. (2014). A systems neuroscience perspective of schizophrenia and bipolar disorder. *Schizophrenia Bulletin, 40*(3), 523-531.

Fregni, F., Boggio, P. S., Nitsche, M. A., Marcolin, M. A., Rigonatti, S. P., & Pascual-Leone, A. (2006a). Treatment of major depression with transcranial direct current stimulation. *Bipolar Disorders, 8*(2), 203-204.

Fregni, F., Boggio, P. S., Nitsche, M. A., Rigonatti, S. P., & Pascual-Leone, A. (2006b). Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression. *Depression and Anxiety, 23*(8), 482-484.

Fregni, F., Nitsche, M. A., Loo, C. K., Brunoni, A. R., Marangolo, P., Leite, J., . . . Bikson, M. (2015). Regulatory considerations for the clinical and research use of transcranial direct current stimulation (tDCS): Review and recommendations from an expert panel. *Clinical Research and Regulatory Affairs, 32*(1), 22-35.

George, M. S., & Aston-Jones, G. (2010). Noninvasive techniques for probing neurocircuitry and treating illness: vagus nerve stimulation (VNS), transcranial

magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). *Neuropsychopharmacology, 35*(1), 301-316.

Gomes, J. S., Shiozawa, P., Dias, A. M., Valverde Ducos, D., Akiba, H., Trevizol, A. P., . . . Cordeiro, Q. (2015). Left dorsolateral prefrontal cortex anodal tDCS effects on negative symptoms in schizophrenia. *Brain Stimulation, 8*(5), 989-991.

Ho, K. A., Bai, S., Martin, D., Alonzo, A., Dokos, S., & Loo, C. K. (2015). Clinical pilot study and computational modeling of bitemporal transcranial direct current stimulation, and safety of repeated courses of treatment, in major depression. *Journal of ECT, 31*(4), 226-233.

Ho, K. A., Bai, S., Martin, D., Alonzo, A., Dokos, S., Puras, P., & Loo, C. K. (2014). A pilot study of alternative transcranial direct current stimulation electrode montages for the treatment of major depression. *Journal of Affective Disorders, 167*, 251-258.

Homan, P., Kindler, J., Federspiel, A., Flury, R., Hubl, D., Hauf, M., & Dierks, T. (2011). Muting the voice: a case of arterial spin labeling-monitored transcranial direct current stimulation treatment of auditory verbal hallucinations. *The American Journal of Psychiatry, 168*(8), 853-854.

Insel, T. R. (2014). A new approach to clinical trials. Retrieved from http://www.nimh.nih.gov/about/director/2014/a-new-approach-to-clinical-trials.shtml

Insel, T. R., & Gogtay, N. (2014). National Institute of Mental Health clinical trials: New opportunities, new expectations. *JAMA Psychiatry, 71*(7), 745-746.

Iuculano, T., & Cohen Kadosh, R. (2013). The mental cost of cognitive enhancement. *The Journal of Neuroscience, 33*(10), 4482-4486.

Jacks, S., Kalivas, B., Mittendorf, A., Kindt, C., & Short, E. B. (2014). Transcranial direct-current stimulation as an adjunct to electroconvulsive therapy and clozapine for refractory psychosis. *The Primary Care Companion for CNS Disorders, 16*(3).

Kadosh, R. C., Levy, N., O'Shea, J., Shea, N., & Savulescu, J. (2012). The neuroethics of non-invasive brain stimulation. *Current Biology, 22*(4), R108-R111.

Kalu, U. G., Sexton, C. E., Loo, C. K., & Ebmeier, K. P. (2012). Transcranial direct current stimulation in the treatment of major depression: A meta-analysis. *Psychological Medicine, 42*(09), 1791-1800.

Kessler, R. C., Demler, O., Frank, R. G., Olfson, M., Pincus, H. A., Walters, E. E., . . . Zaslavsky, A. M. (2005). Prevalence and treatment of mental disorders, 1990 to 2003. *New England Journal of Medicine, 352*(24), 2515-2523.

Khedr, E. M., Elfetoh, N. A., Ali, A. M., & Noamany, M. (2014). Anodal transcranial direct current stimulation over the dorsolateral prefrontal cortex improves anorexia nervosa: A pilot study. *Restorative Neurology and Neuroscience, 32*(6), 789-797.

Klauss, J., Penido Pinheiro, L. C., Silva Merlo, B. L., de Almeida Correia Santos, G., Fregni, F., Nitsche, M. A., & Miyuki Nakamura-Palacios, E. (2014). A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. *International Journal of Neuropsychopharmacology, 17*(11), 1793-1803.

Knotkova, H., Rosedale, M., Strauss, S. M., Horne, J., Soto, E., Cruciani, R. A., . . . Malamud, D. (2012). Using transcranial direct current stimulation to treat depression in HIV-infected persons: The outcomes of a feasibility study. *Frontiers in Psychiatry, 3*(59).

Kuo, M. F., Paulus, W., & Nitsche, M. A. (2014). Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. *Neuroimage, 85*, 948-960.

Kurimori, M., Shiozawa, P., Bikson, M., Aboseria, M., & Cordeiro, Q. (2015). Targeting negative symptoms in schizophrenia: results from a proof-of-concept trial assessing prefrontal anodic tDCS protocol. *Schizophrenia Research, 166*(1-3), 362-363.

Loo, C. K., Alonzo, A., Martin, D., Mitchell, P. B., Galvez, V., & Sachdev, P. (2012). Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. *The British Journal of Psychiatry, 200*(1), 52-59.

Loo, C. K., Sachdev, P., Martin, D., Pigot, M., Alonzo, A., Malhi, G. S., . . . Mitchell, P. (2010). A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression. *International Journal of Neuropsychopharmacology, 13*(1), 61-69.

Martin, D. M., Alonzo, A., Ho, K. A., Player, M., Mitchell, P. B., Sachdev, P., & Loo, C. K. (2013). Continuation transcranial direct current stimulation for the prevention of relapse in major depression. *Journal of Affective Disorders, 144*(3), 274-278.

Martin, D. M., Alonzo, A., Mitchell, P. B., Sachdev, P., Galvez, V., & Loo, C. K. (2011). Fronto-extracephalic transcranial direct current stimulation as a treatment for major depression: An open-label pilot study. *Journal of Affective Disorders, 134*(1-3), 459-463.

Medical Research Council. (2010). Review of mental health research: Report of the strategic review group 2010. Retrieved from http://www.mrc.ac.uk/documents/pdf/mrc-mental-health-research-report-2010/

Meron, D., Hedger, N., Garner, M., & Baldwin, D. S. (2015). Transcranial direct current stimulation (tDCS) in the treatment of depression: Systematic review and meta-analysis of efficacy and tolerability. *Neuroscience and Biobehavioral Reviews, 57*, 46-62.

Mondino, M., Bennabi, D., Poulet, E., Galvao, F., Brunelin, J., & Haffen, E. (2014). Can transcranial direct current stimulation (tDCS) alleviate symptoms and improve cognition in psychiatric disorders? *World Journal of Biological Psychiatry, 15*(4), 261-275.

Mondino, M., Brunelin, J., Palm, U., Brunoni, A. R., Poulet, E., & Fecteau, S. (2015a). Transcranial direct current stimulation for the treatment of refractory symptoms of schizophrenia. Current evidence and future directions. *Current Pharmaceutical Design, 21*(23), 3373-3383.

Mondino, M., Haesebaert, F., Poulet, E., Saoud, M., & Brunelin, J. (2015b). Efficacy of cathodal transcranial direct current stimulation over the left orbitofrontal cortex in a patient with treatment-resistant obsessive-compulsive disorder. *Journal of ECT, 31*(4), 271-272.

Mondino, M., Haesebaert, F., Poulet, E., Suaud-Chagny, M. F., & Brunelin, J. (2015c). Fronto-temporal transcranial Direct Current Stimulation (tDCS) reduces source-monitoring deficits and auditory hallucinations in patients with schizophrenia. *Schizophrenia Research, 161*(2-3), 515-516.

Morse, S. J. (2012). New therapies, old problems, or, a plea for neuromodesty. *AJOB Neuroscience, 3*(1), 60-64.

Murray, C. J. L., Vos, T., Lozano, R., Naghavi, M., Flaxman, A. D., Michaud, C., . . . Lopez, A. D. (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *The Lancet, 380*(9859), 2197-2223.

Nakamura-Palacios, E. M., de Almeida Benevides, M. C., da Penha Zago-Gomes, M., de Oliveira, R. W., de Vasconcellos, V. F., de Castro, L. N., . . . Fregni, F. (2012). Auditory event-related potentials (P3) and cognitive changes induced by frontal direct current stimulation in alcoholics according to Lesch alcoholism typology. *International Journal of Neuropsychopharmacology*, *15*(5), 601-616.

Narayanaswamy, J. C., Jose, D., Chhabra, H., Agarwal, S. M., Shrinivasa, B., Hegde, A., . . . Reddy, Y. C. (2015). Successful application of add-on transcranial direct current stimulation (tDCS) for treatment of SSRI resistant OCD. *Brain Stimulation, 8*(3), 655-683.

Narayanaswamy, J. C., Shivakumar, V., Bose, A., Agarwal, S. M., Venkatasubramanian, G., & Gangadhar, B. N. (2014). Sustained improvement of negative symptoms in schizophrenia with add-on tDCS: A case report. *Clinical Schizophrenia & Related Psychoses, 8*(3), 135-136.

Nawani, H., Bose, A., Agarwal, S. M., Shivakumar, V., Chhabra, H., Subramaniam, A., . . . Venkatasubramanian, G. (2014a). Modulation of corollary discharge dysfunction in schizophrenia by tDCS: Preliminary evidence. *Brain Stimulation, 7*(3), 486-488.

Nawani, H., Kalmady, S. V., Bose, A., Shivakumar, V., Rakesh, G., Subramaniam, A., . . . Venkatasubramanian, G. (2014b). Neural basis of tDCS effects on auditory verbal hallucinations in schizophrenia: A case report evidence for cortical neuroplasticity modulation. *Journal of ECT, 30*(1), e2-4.

Palm, U., Keeser, D., Blautzik, J., Pogarell, O., Ertl-Wagner, B., Kupka, M. J., . . . Padberg, F. (2013). Prefrontal transcranial direct current stimulation (tDCS) changes negative symptoms and functional connectivity MRI (fcMRI) in a single case of treatment-resistant schizophrenia. *Schizophrenia Research, 150*(2-3), 583-585.

Palm, U., Keeser, D., Schiller, C., Fintescu, Z., Reisinger, E., Baghai, T. C., . . . Padberg, F. (2009). Transcranial direct current stimulation in a patient with therapy-resistant major depression. *World Journal of Biological Psychiatry, 10*(4), 632-635.

Palm, U., Schiller, C., Fintescu, Z., Obermeier, M., Keeser, D., Reisinger, E., . . . Padberg, F. (2012). Transcranial direct current stimulation in treatment resistant depression: A randomized double-blind, placebo-controlled study. *Brain Stimulation, 5*(3), 242-251.

Player, M. J., Taylor, J. L., Weickert, C. S., Alonzo, A., Sachdev, P. S., Martin, D., . . . Loo, C. K. (2014). Increase in PAS-induced neuroplasticity after a treatment course of transcranial direct current stimulation for depression. *Journal of Affective Disorders, 167*, 140-147.

Praharaj, S. K., Behere, R. V., & Sharma, P. S. (2015). Cathodal transcranial direct current stimulation over left temporoparietal area for treatment-refractory delusions and auditory hallucinations in schizophrenia: A case study. *Journal of ECT, 31*(4), 277-278.

Price, J. L., & Drevets, W. C. (2013). Neural circuitry of depression. In S. Charney, P. Sklar, J. D. Buxbaum, & E. J. Nestler (Eds.), *Neurobiology of mental illness* (4 ed., pp. 455-469). New York: Oxford University Press.

Rakesh, G., Shivakumar, V., Subramaniam, A., Nawani, H., Amaresha, A. C., Narayanaswamy, J. C., & Venkatasubramanian, G. (2013). Monotherapy with tDCS for Schizophrenia: A Case Report. *Brain Stimulation, 6*(4), 708-709.

Schmidt, L. M., & Gotzsche, P. C. (2005). Of mites and men: Reference bias in narrative review articles: A systematic review. *Journal of Family Practice, 54*(4), 334-338.

Segrave, R. A., Arnold, S., Hoy, K., & Fitzgerald, P. B. (2014). Concurrent cognitive control training augments the antidepressant efficacy of tDCS: A pilot study. *Brain Stimulation, 7*(2), 325-331.

Shahbabaie, A., Golesorkhi, M., Zamanian, B., Ebrahimpoor, M., Keshvari, F., Nejati, V., . . . Ekhtiari, H. (2014). State dependent effect of transcranial direct current stimulation (tDCS) on methamphetamine craving. *International Journal of Neuropsychopharmacology, 17*(10), 1591-1598.

Shenoy, S., Bose, A., Chhabra, H., Dinakaran, D., Agarwal, S. M., Shivakumar, V., . . . Venkatasubramanian, G. (2015). Transcranial direct current stimulation (tDCS) for auditory verbal hallucinations in schizophrenia during pregnancy: A case report. *Brain Stimulation, 8*(1), 163-164.

Shiozawa, P., da Silva, M. E., & Cordeiro, Q. (2015). Transcranial direct current stimulation for treating depression in a patient with right hemispheric dominance: A case study. *Journal of ECT, 31*(3), 201-202.

Shiozawa, P., da Silva, M. E., Cordeiro, Q., Fregni, F., & Brunoni, A. R. (2013a). Transcranial direct current stimulation (tDCS) for catatonic schizophrenia: A case study. *Schizophrenia Research, 146*(1-3), 374-375.

Shiozawa, P., da Silva, M. E., Cordeiro, Q., Fregni, F., & Brunoni, A. R. (2013b). Transcranial direct current stimulation (tDCS) for the treatment of persistent visual and auditory hallucinations in schizophrenia: A case study. *Brain Stimulation, 6*(5), 831-833.

Shiozawa, P., da Silva, M. E., Dias, D. R., Chaves, A. C., de Oliveira Diniz, B. S., & Cordeiro, Q. (2014a). Transcranial direct current stimulation for depression in a 92-year-old patient: A case study. *Psychogeriatrics, 14*(4), 269-270.

Shiozawa, P., Fregni, F., Bensenor, I. M., Lotufo, P. A., Berlim, M. T., Daskalakis, J. Z., . . . Brunoni, A. R. (2014b). Transcranial direct current stimulation for major

depression: An updated systematic review and meta-analysis. *International Journal of Neuropsychopharmacology, 17*(9), 1443-1452.

Shiozawa, P., Leiva, A. P., Castro, C. D., da Silva, M. E., Cordeiro, Q., Fregni, F., & Brunoni, A. R. (2014c). Transcranial direct current stimulation for generalized anxiety disorder: A case study. *Biological Psychiatry, 75*(11), e17-18.

Shiozawa, P., Santos, M. M., Piovesan, F. X., Pellegrinelli, A., Enokibara da Silva, M., Bocato, M. Q., . . . Brunoni, A. R. (2014d). Cerebral blood flow changes after transcranial direct current stimulation for a patient with schizophrenia: A case report. *Journal of Neuropsychiatry and Clinical Neurosciences, 26*(2), E03-05.

Shivakumar, V., Chhabra, H., Subbanna, M., Agarwal, S. M., Bose, A., Kalmady, S. V., . . . Venkatasubramanian, G. (2015). Effect of tDCS on auditory hallucinations in schizophrenia: Influence of catechol-O-methyltransferase (COMT) Val158Met polymorphism. *Asian Journal of Psychiatry, 16*, 75-77.

Shivakumar, V., Narayanaswamy, J. C., Agarwal, S. M., Bose, A., Subramaniam, A., & Venkatasubramanian, G. (2014). Targeted, intermittent booster tDCS: a novel add-on application for maintenance treatment in a schizophrenia patient with refractory auditory verbal hallucinations. *Asian Journal of Psychiatry, 11*, 79-80.

Smith, R. C., Boules, S., Mattiuz, S., Youssef, M., Tobe, R. H., Sershen, H., . . . Davis, J. M. (2015). Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: A randomized controlled study. *Schizophrenia Research, 168*(1-2), 260-266.

Thomas, B. H., Ciliska, D., Dobbins, M., & Micucci, S. (2004). A process for systematically reviewing the literature: Providing the research evidence for public health nursing interventions. *Worldviews on Evidence-Based Nursing, 1*(3), 176-184.

Tortella, G., Casati, R., Aparicio, L. V. M., Mantovani, A., Senço, N., D'Urso, G., . . . Brunoni, A. R. (2015). Transcranial direct current stimulation in psychiatric disorders. *World Journal of Psychiatry, 5*(1), 88-102.

Valiengo, L., Bensenor, I. M., Goulart, A. C., de Oliveira, J. F., Zanao, T. A., Boggio, P. S., . . . Brunoni, A. R. (2013). The Sertraline versus Electrical Current Therapy for Treating Depression Clinical Study (select-TDCS): Results of the crossover and follow-up phases. *Depression and Anxiety, 30*(7), 646-653.

Venkatakrishnan, A., & Sandrini, M. (2012). Combining transcranial direct current stimulation and neuroimaging: Novel insights in understanding neuroplasticity. *Journal of Neurophysiology, 107*(1), 1-4.

Volpato, C., Piccione, F., Cavinato, M., Duzzi, D., Schiff, S., Foscolo, L., & Venneri, A. (2013). Modulation of affective symptoms and resting state activity by brain stimulation in a treatment-resistant case of obsessive-compulsive disorder. *Neurocase, 19*(4), 360-370.

Wagner, T., Valero-Cabre, A., & Pascual-Leone, A. (2007). Noninvasive human brain stimulation. *Annual Review of Biomedical Engineering, 9*, 527-565.

Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., . . . Vos, T. (2013). Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. *The Lancet, 382*(9904), 1575-1586.

Widdows, K. C., & Davis, N. J. (2014). Ethical considerations in using brain stimulation to treat eating disorders. *Frontiers in Behavioral Neuroscience, 8*, 1-4.

Wittchen, H. U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jonsson, B., . . . Steinhausen, H. C. (2011). The size and burden of mental disorders and other

disorders of the brain in Europe 2010. *European Neuropsychopharmacology*, *21*(9), 655-679.

Wokke, M. E., Talsma, L. J., & Vissers, M. E. (2014). Biasing neural network dynamics using non-invasive brain stimulation. *Frontiers in Systems Neuroscience*, *8*, 246.

Wolkenstein, L., & Plewnia, C. (2013). Amelioration of cognitive control in depression by transcranial direct current stimulation. *Biological Psychiatry*, *73*(7), 646-651.

Chapter 3. The effects of prefrontal cortex transcranial direct current stimulation on food craving and temporal discounting in women with frequent food cravings

---

Kekic, M., McClelland, J., Campbell, I. C., Nestler, S., Rubia, K., David, A. S., & Schmidt, U. (2014). The effects of prefrontal cortex transcranial direct current stimulation (tDCS) on food craving and temporal discounting in women with frequent food cravings. *Appetite, 78,* 55-62.

3.1 ABSTRACT

Obesity and eating disorders, such as bulimia nervosa (BN) and binge-eating disorder (BED), can be conceptualised as forms of addiction. Food cravings are thought to precipitate the compulsive overeating that is seen in these conditions. Transcranial direct current stimulation (tDCS) has been used to suppress food cravings, but there is insufficient evidence to support its application in clinical practice. Furthermore, the potential moderating role of impulsivity has not been considered. This study employed a randomised within-subjects crossover design to examine whether a 20-minute session of placebo-controlled bilateral tDCS to the dorsolateral prefrontal cortex (DLPFC) (anode right/cathode left) would transiently modify food cravings and temporal discounting (TD; a measure of choice impulsivity) in 17 healthy women with frequent food cravings. Whether the effects of tDCS on food cravings were moderated by individual differences in TD behaviour was also explored. Participants were exposed to real food and to a film of people eating, and food cravings and TD were assessed before and after active and sham stimulation. Craving for sweet but not savoury foods was reduced following real tDCS. In addition, participants who exhibited more reflective choice behaviour were more susceptible to the anti-craving effects of tDCS than those who displayed more impulsive choice behaviour. No differences were seen in TD or actual food consumption after real versus sham tDCS. These findings support the efficacy of tDCS interventions in temporarily lowering food cravings and identify the moderating role of intertemporal choice behaviour.

3.2 INTRODUCTION

It has been proposed that certain foods – particularly those high in sugar – are addictive, and that obesity and eating disorders, such as bulimia nervosa (BN) and binge-eating disorder (BED), can be conceptualised as forms of addiction (Avena et al., 2009). Food cravings (intense urges to consume particular foods) are thought to precipitate the compulsive overeating that characterises these conditions, and have been positively associated with binge-eating (Ng & Davis, 2013), daily calorie intake (Lafay et al., 2000), BMI (Franken & Muris, 2005), daytime sleep (Landis et al., 2009), and dieting failure (Meule et al., 2011). There is also evidence that excessive craving for sweet foods is associated with drug and alcohol abuse (for a review see Pelchat, 2002).

Extensive behavioural and neurobiological data indicate many commonalities between food craving and drug craving (for a review see Pelchat, 2009). For instance, both lead to foraging and ingestion habits that persist and strengthen despite the threat of negative health and social consequences (Volkow & Wise, 2005) and, furthermore, cravings can predict both relapse to drug taking in abstinent substance users (Rosenberg, 2009) and weight regain after bariatric surgery in obese patients (Odom et al., 2010). The neurotransmitter systems implicated in food craving overlap substantively with those involved in drug craving; for example, exposure to both food and drug craving-provoking stimuli is associated with increased levels of reward circuitry dopaminergic activation in the brain (Blum et al., 2011). Food craving and drug craving are also mediated by shared functional neuroanatomy. Several brain regions appear to be involved (for a review see Tang et al., 2012), but most data suggest that the left, right, or bilateral dorsolateral prefrontal cortex (DLPFC; an area in the prefrontal cortex important for executive functioning) is activated in response to cues that induce both food (Siep et al., 2009; Gearhardt et al., 2011) and drug cravings (Maas et al., 1998;

Bonson et al., 2002; Hayashi et al., 2013). The level of cue-elicited prefrontal activation can predict prospective food intake (Cornier et al., 2010) and drug use (Grüsser et al., 2004), and appears to be altered in compulsive overeaters (Schienie et al., 2009) and drug-addicted individuals (Wexler et al., 2001; Yalachkov et al., 2009) compared with healthy controls. A deficiency in the prefrontal cortical inhibitory networks might therefore contribute to the pathophysiology of disordered eating and substance use disorders.

A growing number of studies have sought to directly manipulate DLPFC activation as a means of reducing cravings. Two non-invasive brain stimulation (NIBS) methods have been used, both of which are well-tolerated, have minimal side effects, and do not require surgical procedures. Repetitive transcranial magnetic stimulation (rTMS) employs an electromagnetic field generated by a figure-eight coil to suppress (low-frequency) or enhance (high-frequency) cortical excitability in a localised area of the brain (McClelland et al., 2013a). Alternatively, transcranial direct current stimulation (tDCS) involves the delivery of a weak electrical current via two surface electrodes; anodal and cathodal tDCS cause excitatory and inhibitory effects on underlying cortical neurons, respectively (McClelland et al., 2013a).

Research has consistently shown that NIBS can reduce drug craving in laboratory settings; cue-provoked cravings for cocaine, alcohol, and nicotine have been transiently lowered with a single session of rTMS or tDCS to the left or right DLPFC (Camprodon et al., 2007; Boggio et al., 2008; Fregni et al., 2008b; Mishra et al., 2010; Li et al., 2013). Emerging evidence indicates that NIBS can also temporarily lower cravings for foods (for reviews see Jansen et al., 2013; McClelland et al., 2013a). In the earliest of these studies, Uher and colleagues (2005) showed that a single session of high-

frequency rTMS to the left DLPFC suppressed cravings in healthy women with frequent food cravings. This finding was later replicated by two studies using bilateral DLPFC tDCS (anode right/cathode left), the former also showing a reduction in calories ingested following active versus sham stimulation (Fregni et al., 2008a; Goldman et al., 2011). The effects of prefrontal cortex modulation have also been investigated in a clinical sample; Van den Eynde et al. (2010) found that high-frequency rTMS to the left DLPFC lowered cue-induced food cravings in patients with a bulimic disorder.

Although the anti-craving effects recorded in these experiments were temporary (the effects of a single session of rTMS or tDCS are expected to last for up to two hours, depending on the parameters used; Nitsche et al., 2001; Hoogendam et al., 2010), it is possible that NIBS delivered over extended periods of time could induce longer-lasting behavioural responses through changes in neuroplasticity. Indeed, interventions comprising multiple sessions of NIBS have shown therapeutic potential for a range of conditions including BN (Downar et al., 2012), anorexia nervosa (McClelland et al., 2013b), and substance use disorder (Politi et al., 2008). Moreover, rTMS is an approved second-line treatment for major depressive disorder in many countries including the UK and US. Given that food cravings play a central role in obesity and some eating disorders, the potential for NIBS to enduringly suppress these cravings represents an exciting prospect.

Whilst the tendency to overeat or binge-eat can be influenced by food cravings, Davis et al. (2004) point out that "human overeating is not just a passive response to...powerful physiological drives; it is also about making choices" (p. 929). It is well-established that drug addicts have maladaptive decision-making capabilities (for a review see Dom et al., 2005), and the same applies to compulsive overeaters. Specifically, obese people

and patients with BED show steeper rates of temporal discounting (TD; Weller et al., 2008; Davis et al., 2010) – an experimental proxy of aspects of impulsivity such as temporal foresight and delay of gratification. In the context of eating, these individuals struggle to defer food gratification in the interest of future health or aesthetics. Evidence shows that the capacity for self-control in reward-related decision-making tasks – including TD – depends crucially on DLPFC activity levels (Clark et al., 2003; Hare et al., 2009; Christakou et al., 2011). Furthermore, reduced prefrontal reactivity during a TD task has been found to predict a greater rate of weight gain in obesity (Kishinevsky et al., 2012). It is possible that NIBS could reduce overeating behaviours by simultaneously suppressing food cravings and improving intertemporal decision-making. Indeed, Figner et al. (2010) showed that low-frequency rTMS delivered to the left DLPFC altered the discounting of delayed rewards in healthy adults. Nevertheless, to our knowledge the relationship between the DLPFC, food craving, and TD behaviour is yet to be explored.

This study investigated whether bilateral manipulation of the DLPFC with tDCS modulates food craving-related thoughts and behaviours in healthy women who experience frequent food cravings. tDCS was chosen because of its practical advantages over rTMS (e.g., it is simpler, safer, and less expensive; Poreisz et al., 2007; Priori et al., 2009), and because its efficacy in lowering food cravings has been demonstrated in two non-clinical samples comparable to our own (Fregni et al., 2008a; Goldman et al., 2011). Unlike these studies, however, we also included a measure of choice impulsivity. The main aims were to establish whether: (1) one session of sham-controlled tDCS (anode over the right DLPFC and cathode over the left DLPFC) would temporarily reduce food cravings; (2) this session of tDCS would transiently alter TD behaviours; and (3) the effects of tDCS on food cravings are moderated by individual differences in

intertemporal decision-making abilities. Based on Fregni et al.'s (2008a) finding, we also speculated that actual food consumption in a free-eating task might decrease following active versus sham stimulation.

3.3 MATERIALS AND METHODS

3.3.1 Participants

Healthy female volunteers who self-identified as having frequent food cravings (≥ 1 per day, assessed by self-report questionnaire) aged 18-60 were recruited from the King's College London (KCL) recruitment webpage. Respondents were screened by phone and were excluded if they: (a) smoked > 10 cigarettes per day; (b) drank > the recommended daily alcohol intake (3-4 units for men and 2-3 units for women; National Health Service [NHS], 2013); (c) used illicit drugs; (d) had a current major psychiatric disorder; (e) had a current or past history of an eating disorder; (f) had any significant health problems in the previous 6 months; (g) had a personal or family history of seizures; (h) had a history of stroke; (i) had a history of head injury or neurosurgery; (j) had any implanted metal devices; (k) suffered from frequent or severe headaches; (l) were taking any medications associated with lowered seizure threshold; (m) were pregnant or sexually active and not using contraception; (n) were allergic to any of the foods presented in the study; or (o) gave any threshold answers in the Structured Clinical Interview for Diagnostic and Statistical Manual (*DSM*) Axis I Disorders (SCID-I; First et al., 2002).

Twenty-eight women completed the telephone screen and 25 fulfilled all inclusion/exclusion criteria. Of these, 20 completed both study sessions – 4 withdrew before the first visit and 1 experienced skin irritation so did not return for the second

appointment. The data of three participants were excluded due to their responses in baseline assessments completed in the laboratory – two had clinically significant global scores (≥ 4; Rø et al., 2012) on the Eating Disorder Examination Questionnaire (EDE-Q; Fairburn & Beglin, 1994) and one had moderate scores on all three dimensions of the Depression Anxiety and Stress Scale (DASS-21; Lovibond & Lovibond, 1995). The final sample included in the analyses consisted of 17 females aged 19-55 (*M* = 26.41, *SD* = 8.30) who were predominantly Caucasian (70.6%). Participants reported experiencing an average of 3.15 (*SD* = 1.41, range = 1-5.5) food cravings per day and the majority (82.4%) primarily craved sweet foods. The mean BMI was 23.81 (*SD* = 2.60, range = 19.85-29.28); 70.6% of participants were in the healthy range (18.5-24.9) and 29.4% were overweight (25-25.9) (NHS, 2012). All participants were educated to A-level standard or higher. See Table 3.1 for more participant characteristics.

The study was carried out at the Institute of Psychiatry, KCL (London, UK). Ethical approval was obtained from the KCL Psychiatry, Nursing and Midwifery Research Ethics Subcommittee. All participants provided written informed consent and were debriefed fully at the end of the experiment.

Table 3.1 Baseline characteristics of participants.

Characteristic	Mean	SD	Range
Age	26.41	8.31	19.00 - 55.00
BMI	23.81	2.60	19.90 - 29.30
DASS-21 depression	3.88	4.33	0.00 - 14.00
DASS-21 anxiety	2.12	2.40	0.00 - 8.00
DASS-21 stress	7.18	4.53	0.00 - 18.00
Global EDE-Q	1.46	0.98	0.49 - 3.88
Global FCQ-T	118.47	18.46	91.00 - 151.00
Cravings per day[a]	3.15	1.36	1.00 - 5.50
Baseline *k*-value	8.05	9.86	0.91 - 39.92

SD, standard deviation; BMI, body mass index; DASS-21, 21-item Depression, Anxiety and Stress Scale; EDE-Q, Eating Disorders Examination Questionnaire; FCQ-T, Food Craving Questionnaire-Trait.

[a] Assessed with self-report demographic questionnaire ("How many food cravings do you experience per day?")

3.3.2 Design and procedure

This study employed a double-blind sham-controlled within-subjects crossover design in which all participants received real and sham tDCS. Order of stimulation was randomised and counterbalanced across participants using STATA® software (to allow for experimenter blinding, real and sham stimulation were encoded with five-digit numbers which were assigned to each session by a third party). An intersession interval ($\geq$ 48 hours) was used to avoid any carryover effects due to stimulation and, where possible, both sessions were held at the same time of day (difference between time of day of real and sham session: M = 61 minutes, SD = 121 minutes).

Upon arrival to the first appointment only, participants completed a battery of baseline assessments (demographic questionnaire, EDE-Q, DASS-21, Food Craving

Questionnaire-Trait [FCQ-T; Cepeda-Benito et al., 2000]). A 10cm continuous visual analogue scale (VAS) measuring baseline hunger was administered at the start of both sessions, followed by several pre-tDCS measures in the following order: (1) Food Challenge Task (FCT); (2) Food Craving Questionnaire-State (FCQ-S); (3) saliva sample; and (4) TD task. Participants then received a 20-minute tDCS session (real or sham). Immediately after this (post-tDCS), they repeated the pre-tDCS measures in the following order: (1) TD task; (2) FCT; (3) FCQ-S; and (4) saliva sample. Participants then engaged in a free-eating task. At the end of the second appointment only, we evaluated the tolerability of the intervention and the success of the blinding procedure. All instruments used in the protocol have sound psychometric properties.

3.3.3 Food Challenge Task

This is a behavioural measure – used to induce and assess food cravings – which was developed and administered previously in our laboratory (Uher et al., 2005; Van den Eynde et al., 2010, 2013), and adapted for use in the current study. Two short films (< 3 minutes each) of adults eating energy-dense foods (chocolates, crisps, nuts, and biscuits) were shown to participants consecutively, and the same foods were present in the room. After the films, participants rated their attitude towards food intake and their emotional state on a series of 10cm continuous VASs measuring appearance, smell, taste, and urge to eat for each food separately, as well as hunger, general urge to eat, general urge to binge, stress, anxiety, tension, and mood. The primary outcome variable in the analyses (global FCT score) was computed by totalling the ratings on all VASs relating to food intake except for hunger. This is because food cravings tend to be hedonically driven and are unrelated to an individual's physiological needs (Pelchat et al., 2004; Davis et al., 2010).

3.3.4 Food Craving Questionnaire-State

This is a self-report inventory used to assess food craving as a psychological state in response to specific situations, which was developed for use among average-weight adults (Cepeda-Benito et al., 2000). The instrument contains 15 items organised into 5 subscales. Responses are made on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree), yielding a global score and a score for each dimension.

3.3.5 Hormonal stress response (saliva sample)

To assess whether tDCS had an effect on the hypothalamus-pituitary-adrenal (HPA) axis stress response we collected salivary cortisol samples. Participants chewed on a 3x1cm inert polymer oral swab (Salivette®) for 1 minute, which was then placed into a capped centrifuge tube. Samples were stored at -20°C – where they remain stable for up to 3 months (Garde & Hansen, 2005) – and were analysed for cortisol using competitive immunoassays (Salimetrics® salivary ELISA kits). Data indicate that cortisol measurement with Salivettes® is a reliable prediction method of total and calculated free serum cortisol levels (Poll et al., 2007).

3.3.6 Temporal discounting task

Choice impulsivity was assessed with a computerised hypothetical monetary TD task, which measures the degree to which a reward is subjectively discounted in relation to its temporal delay (Rubia et al., 2009). A monetary task was used because food TD tasks present several difficulties (e.g., the reinforcing value of food is not linear and food preferences are highly variable) and because compulsive overeaters appear to have a general tendency to make impulsive choices, which is not specific to choices about

food[10] (Manwaring et al. 2011). Participants chose between a smaller amount of money (between £0 and £100) available immediately, and a larger amount (always £100) available after 1 week, 1 month, 1 year, or 2 years (25 trials for each delay). The value of the immediate reward was adjusted in an algorithm based on previous choices; this narrowed the range of the immediate values offered until an amount was reached that the participant judged as equivalent to the fixed delayed reward (Richards et al., 1999). This point of subjective equality is referred to as the indifference point. A hyperbolic decay function was fitted to the indifference point for each delay to describe the relationship between the subjective value of a reward as a function of the delay to its presentation. The mathematical expression of this relationship is $V = A/(1 + kD)$, where V is the subjective value of a reward of amount A, D is the delay to reward presentation, and k is a constant characterising the individual's rate of discounting (Rachlin et al., 1991). The value of k is frequently used as the main dependent variable in the TD paradigm, and is considered an experimental proxy of aspects of impulsivity such as temporal foresight and delay of gratification. Participants with larger k-values show greater TD – for them rewards given after a delay lose more subjective value.

3.3.7 Real transcranial direct current stimulation

A single 20-minute session of tDCS was delivered using a neuroConn® DC-STIMULATOR device at a constant current of 2 mA (with a 10-second fade in/out) using two 25 cm^2 surface sponge electrodes soaked in a sterile saline solution (0.9% sodium chloride). At least 50% of this transcranially applied current is expected to enter the brain through the skull (Nitsche et al., 2008). The anode and cathode were placed

[10] Women with BED discounted both monetary and directly consumable rewards (food, massage time, preferred sedentary activity) more steeply than obese and control groups.

over the right (F4) and left (F3) DLPFC, respectively. The sites of interest were located using the International EEG 10-20 system. The tDCS parameters used have been shown to be safe in healthy individuals (Iyer et al., 2005) and the charge density was two magnitudes lower than the experimentally determined threshold estimate in rats (Liebetanz et al., 2009). tDCS is generally well-tolerated and is associated with relatively minor side effects; a mild tingling sensation is the most commonly reported adverse effect (Poreisz et al., 2007). We assessed tolerability via salivary cortisol and a 10cm continuous VAS measuring discomfort during the procedure.

3.3.8 Sham transcranial direct current stimulation

The electrode placement for sham tDCS was the same as for active tDCS; however, the stimulation automatically turned off after 30 seconds. Participants therefore experienced the initial itching sensation but received no current for the rest of the 20-minute session. Research shows that this method for sham tDCS is reliable and cannot easily be distinguished from real tDCS by participants or investigators (Gandiga et al., 2006). The validity of the sham treatment was assessed by asking participants to guess which session they thought was a placebo, and to rate their confidence in this guess on a 10cm continuous VAS.

3.3.9 Free-eating task

To measure actual food consumption after real and sham tDCS, weights of foods presented in the FCT were recorded before and after each laboratory session. After the final post-tDCS measure, the experimenter left the room for 3 minutes and invited the participant to help themselves to any of the foods while they were gone. The percentage eaten was calculated for each food separately and for all foods together.

3.4 RESULTS

Statistical analyses were performed using IBM® SPSS® software (Version 20). For variables with normally distributed data, the effects of active versus sham tDCS were evaluated using two-way 2 (stimulation: real vs. sham) x 2 (timepoint: pre-tDCS vs. post-tDCS) repeated measures ANOVAs, whereby a significant stimulation x timepoint interaction indicated a difference in the effect that real and sham tDCS had on pre-tDCS scores. Where data were not normally distributed, non-parametric alternatives were employed. All statistical tests were two-tailed and the level of significance was set at $\alpha = 0.05$.

3.4.1 Food cravings and transcranial direct current stimulation

When compared to sham stimulation, real stimulation did not alter global FCT scores [$F(1, 16) = 0.74$, *ns*]. There was a significant stimulation x timepoint interaction for global FCQ-S score [$F(1, 16) = 5.02$, $p < .05$] in the opposite direction to that expected; pre-tDCS scores were lowered more by sham (M = -11.32%, SD = 21.12%) than by real stimulation (M = -1.94%, SD = 21.36%). However, this finding is largely attributable to scores on FCQ-S subscale 5 (craving as a physiological state) as the global FCQ-S interaction term was not significant when this subscale was excluded from the analysis [$F(1, 16) = 3.19$, *ns*].

3.4.2 Food cravings for specific food groups and transcranial direct current stimulation

To examine the effect of tDCS on cravings for specific food groups, we analysed FCT ratings (appearance, smell, taste, urge to eat) for sweet (chocolate and biscuits) and

savoury (crisps and nuts) foods separately. A significant stimulation x timepoint interaction was observed for sweet [$F(1, 16) = 4.59$, $p < .05$] but not savoury foods [$F(1, 16) = 2.20$, *ns*]. Cravings for sweet foods were reduced more by real (M = -13.31%, SD = 34.73%) than by sham tDCS (M = -6.06%, SD = 29.86%), whilst cravings for savoury foods were lowered by comparable amounts in both conditions (real: M = -9.29%, SD = 36.84%, sham: M = -10.30%, SD = 30.46%) (Figure 3.1).

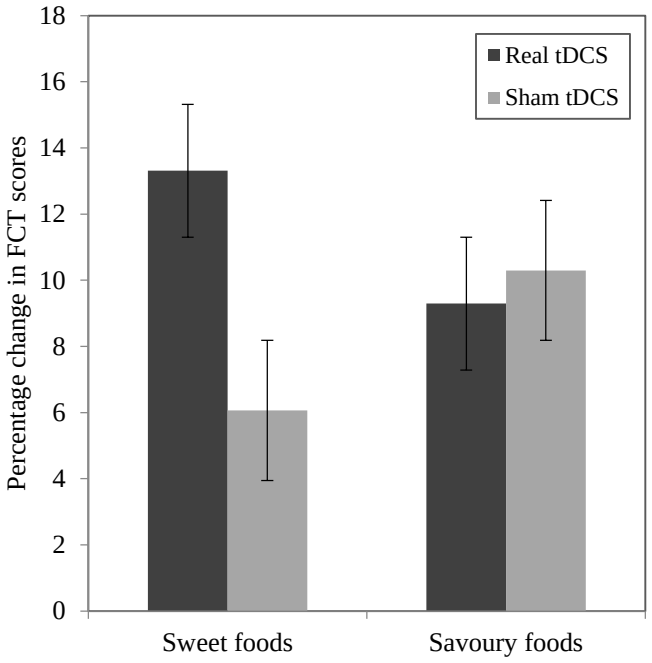


Figure 3.1 Mean percentage change in Food Challenge Task scores (appearance, smell, taste, urge to eat) for sweet and savoury foods in real and sham transcranial direct current stimulation conditions.

FCT, Food Challenge Task; tDCS, transcranial direct current stimulation.

Note: Error bars represent ± SE.

3.4.3 Temporal discounting and transcranial direct current stimulation

Since *k*-values on the TD task were not normally distributed, the effect of tDCS on intertemporal choice behaviour was evaluated using paired-samples Wilcoxon signed-

rank tests. Post-tDCS *k*-values did not differ significantly from pre-tDCS *k*-values following real [z = -0.45, *ns*] or sham stimulation [z = -0.31, *ns*].

3.4.4 Interaction between temporal discounting, food cravings, and transcranial direct current stimulation

To establish whether the effects of tDCS on food cravings were moderated by individual differences in intertemporal decision-making abilities, we performed the analyses with baseline *k*-value (calculated as the mean of the two pre-tDCS *k*-values) as a covariate. Results showed a significant stimulation x timepoint interaction for global FCT score [$F(1, 15) = 4.82$, $p < .05$]; after controlling for baseline *k*-value there was a sharper decrease in global FCT scores following real tDCS than following sham tDCS. In addition, the stimulation x timepoint interaction for global FCQ-S score was no longer significant [$F(1, 15) = 0.18$, *ns*].

There was also a significant stimulation x timepoint x baseline *k*-value interaction for global FCT score [$F(1, 15) = 5.12$, $p < .05$] and global FCQ-S score [$F(1, 15) = 5.60$, $p < .05$]. Participants with lower baseline *k*-values – and greater intertemporal decision-making abilities – were more susceptible to the anti-craving effects of active tDCS. Conversely, baseline *k*-value did not moderate the effects that sham tDCS had on food cravings. To illustrate this graphically, we divided participants into two groups according to their baseline *k*-value; participants with baseline *k*-values in the first or second quartiles (n = 9) were classified as showing low TD (more reflective choice behaviour) whilst those with baseline *k*-values in the third or fourth quartiles (n = 8) were categorised as showing high TD (more impulsive choice behaviour) (Figure 3.2).

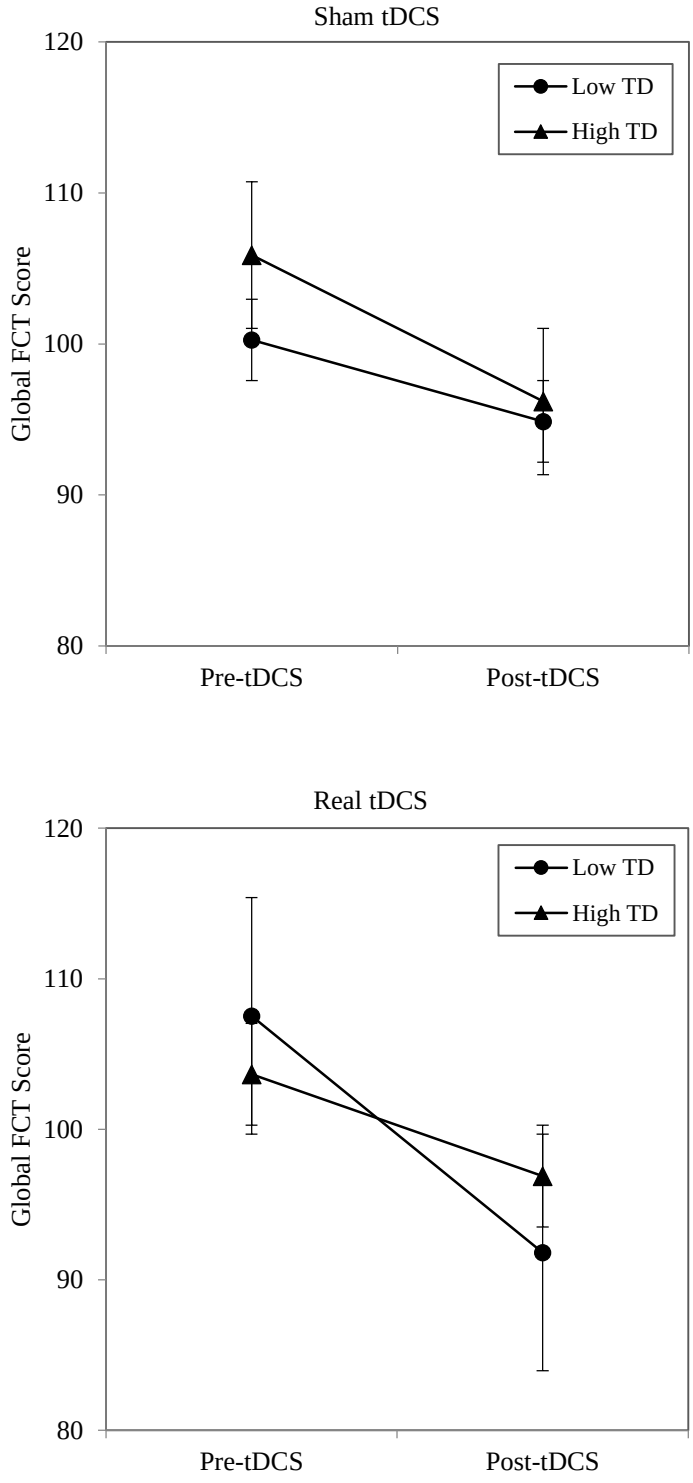


Figure 3.2 Mean pre- and post- transcranial direct current stimulation (tDCS) global Food Challenge Task scores for participants showing high and low temporal discounting in real and sham tDCS conditions.

FCT, Food Challenge Task; TD, temporal discounting; tDCS, transcranial direct current stimulation.

3.4.5 Actual food consumption and transcranial direct current stimulation

Values for the amount of food consumed during the free-eating task were not normally distributed, and were therefore analysed using paired-samples Wilcoxon signed-rank tests. Results showed no significant difference in the proportion of chocolate, crisps, nuts, biscuits, or total food ingested after real versus sham tDCS [zs < -1.04, ps > .30]. These results were not confounded by baseline hunger which was stable across the two conditions [$t(16) = -0.67$, *ns*].

3.4.6 Success of blinding procedure

Participants were not able to distinguish real stimulation from sham stimulation at a rate better than chance [$X^2(1) = 2.88$, *ns*]. Furthermore, the mean confidence rating for this guess on a 10cm continuous VAS was 5.04 (SD = 3.12, range = 0.0-9.7), indicating that participants were not particularly certain that their guess was accurate. The order in which participants received real and sham stimulation did not affect their ability to identify the placebo session [p = .29; Fisher's exact test].

3.4.7 Tolerability and safety of transcranial direct current stimulation

One participant withdrew from the study after the first appointment due to skin irritation at the site of stimulation. Another participant reported developing a slight headache following active tDCS which subsided without treatment. Overall, the intervention was well-tolerated and participants reported experiencing minimal discomfort (10cm VAS: M = 2.64, SD = 2.51, range = 0-7.7). When compared to sham tDCS, real tDCS did not have any adverse effects on the HPA axis stress response [$F(1, 15) = 0.29$, *ns*] and did not alter self-reported stress, anxiety, tension, or mood [Fs < 0.55, ps > .47].

3.4.8 Order effects

There was evidence of an order effect whereby, following real stimulation, participants allocated to the real/sham condition displayed a sharp decrease in global FCT scores whereas those in the sham/real condition showed a marginal increase in scores [$F(1, 15) = 7.17$, $p < .05$]. Participants who received real tDCS first ($n = 8$) did not differ significantly from those who received sham tDCS first ($n = 9$) in any baseline measures [Fs < 3.89, ps > .08].

3.5 DISCUSSION

The present study investigated the effects of a single session of sham-controlled tDCS (anode over the right DLPFC, cathode over the left DLPFC) on food cravings, intertemporal choice behaviour, and actual food consumption in healthy women with frequent food cravings. The key findings were that tDCS reduced cravings for sweet but not savoury foods, and that participants who exhibited more reflective choice behaviour were more susceptible to the anti-craving effects of tDCS than those who displayed more impulsive choice behaviour.

The observed decrease in craving for sweet foods is consistent with numerous accounts of prefrontal cortex tDCS transiently lowering food and drug cravings (Boggio et al., 2008; Fregni et al., 2008a; Fregni et al., 2008b; Goldman et al., 2011), and provides evidence that food craving is associated with DLPFC activity. This brain region is thought to regulate cravings by integrating information relating to cues, cravings, motivation, and expectancy (McBride et al., 2006). By combining rTMS with functional magnetic resonance imaging (fMRI), Hayashi et al. (2013) formulated a two-stage

model of cue-reactivity whereby the medial orbitofrontal cortex (mOFC) encodes the subjective value of the drug (or food) and the DLPFC incorporates intertemporal availability and cue information to modulate the presumed mOFC value signal.

The mechanisms by which DLPFC stimulation lowers cravings are unknown, although data suggest that reduced function in the right prefrontal cortex may lead to overeating (Alonso-Alonso & Pascual-Leone, 2007). Interestingly, however, NIBS appears to suppress cravings even when the right DLPFC is inhibited and/or the left DLPFC is excited (Uher et al., 2005; Boggio et al., 2008; Fregni et al., 2008a; Fregni et al., 2008b; Van den Eynde et al., 2010). It has therefore been proposed that state craving depends on a bilateral balance between left and right DLPFC activity, and that any disruption to this balance will cause cravings to subside (Boggio et al., 2008). DLPFC modulation might also lead to craving inhibition by indirectly altering the activity level of the mOFC.

That tDCS suppressed cravings for sweet but not savoury foods is in approximate agreement with Goldman et al.'s (2011) findings, and provides an explanation as to why global FCQ-S and global FCT scores were not reduced by tDCS. It is possible that the mechanisms underlying cravings for sweet and savoury foods are different; several lines of evidence support this interpretation. Firstly, the concept of sweet food addiction is frequently likened to drug addiction (e.g., Avena et al., 2008), whereas parallels have not been drawn between drug addiction and addiction to savoury foods. Secondly, chocolate contains several biologically active constituents – which are not found in savoury foods – that can cause psychological sensations comparable to those of other addictive substances (Bruinsma & Taren, 1999). Thirdly, sweet foods generally contain higher sugar concentrations than savoury foods, and sugar is known to have addictive

potential because it releases opioids and dopamine (Avena et al., 2008). Finally, ample data – including that in this study – indicate that cravings for sweet foods are stronger and more prevalent than cravings for savoury foods (Yanovski, 2003; Hill, 2007).

The present study demonstrates that inter-individual differences in intertemporal decision-making abilities moderate the anti-craving effects of prefrontal cortex tDCS. Specifically, participants who exhibited more impulsive choice behaviours showed a smaller reduction in cravings following active stimulation than those who displayed more reflective choice behaviours. This is unsurprising since individuals with a strong tendency to devalue delayed rewards are expected to hold particularly disinhibited attitudes towards food intake (Davis et al., 2010), and dimensions of impulsivity have also been found to negatively predict outcomes of existing treatments for binge eating (Manasse et al., 2016). Unlike Figner et al. (2010), we did not observe significant changes in TD following DLPFC modulation. It may be that an individual's ability to delay gratification cannot be easily modified with NIBS; indeed, only one study has demonstrated otherwise and, moreover, the capacity for adaptive intertemporal decision-making is not a capricious psychological state but rather a stable personality trait (Davis et al., 2010). Alternatively, the TD task employed may have lacked sensitivity since all trials used 'Accelerate' framing (i.e., when the value of the delayed reward is fixed), which is associated with decreased discounting relative to 'Delay' framing (i.e., when the value of the immediate reward is fixed; Steinglass et al., 2012).

In our study, real versus sham tDCS did not affect the amount of food consumed in the free-eating task. Although Fregni et al. (2008a) reported reduced caloric ingestion following active stimulation, Goldman et al. (2011) did not replicate this result. It is possible that the observed reduction in self-reported craving did not translate into an

equipollent reduction in food consumption because the free-eating session lacked ecological validity; eating behaviours displayed in this task are unlikely to mirror those engaged in on a daily basis, particularly if participants suspected that their food consumption was being recorded. Goldman et al. (2011) suggested instead performing "a natural observation of food consumption during a mealtime later in the day or the following day" (p. 745); however, the tDCS parameters used are not expected to have such a lasting effect. It might therefore prove more beneficial to revise the experimental free-eating task to improve its generalisability; for example, it could take place in a more natural setting and its length could be increased.

This study has some limitations; for example, we observed an order effect whereby real tDCS only reduced food cravings for participants who received real stimulation during their first session. One explanation for this draws on the finding that cue-induced craving for cigarettes was dramatically increased when people were told they could smoke immediately after testing (Hayashi et al., 2013). In our study, participants were not informed prior to testing that they would be given *ad libitum* access to a selection of foods; therefore, they would have only anticipated the free-eating task during their second visit, once they were familiarised with the experimental procedure. This anticipation might have potentiated cravings in the second session, making them less susceptible to modulation by tDCS. We did not ask participants to fast prior to their scheduled sessions. Although hunger is not a necessary prerequisite for food craving (Pelchat et al., 2004), similar studies have required that participants refrain from eating and drinking (except water) for several hours before testing (Uher et al., 2005; Van den Eynde et al., 2010; Goldman et al., 2011). Nevertheless, our results showed that baseline hunger was stable across conditions. We also did not collect data on menstrual phase despite evidence that it influences food craving (Davidsen et al., 2007); however,

not all studies of NIBS and food craving have addressed this issue (Fregni et al., 2008; Van den Eynde et al., 2010). In addition, we did not measure IQ or income which may influence TD of monetary rewards (Green et al., 1996; de Wit et al., 2007), though this is unlikely to have impacted the results since each participant served as their own control. A final limitation is that we did not include an anode left/cathode right tDCS condition, which would have helped to clarify whether there is a hemispheric laterality for food craving.

The present research has some important implications. Although the anti-craving effects observed here were presumably only temporary, it is possible that NIBS delivered over longer periods of time could elicit more sustained reductions in food craving. tDCS is an appealing technique because it is inexpensive, easy to administer, non-invasive, and painless. Future research should evaluate the therapeutic potential of tDCS for eliminating problematic overeating and binge-eating behaviours by analysing the effects of repeated DLPFC stimulation. The inter-individual differences we detected in a participant's susceptibility to the anti-craving effects of stimulation suggest that, if developed into a treatment for compulsive overeating, tDCS might be less effective for patients with poorer intertemporal decision-making abilities (e.g., those with clinical eating disorders; Davis et al., 2010). It may be possible to teach these individuals more adaptive strategies to prepare them for a tDCS intervention.

In summary, our data contribute to the growing body of literature demonstrating that a single session of active tDCS to the DLPFC can temporarily suppress food craving. Our results support those of Fregni et al. (2008) and Goldman et al. (2011), and extend them by suggesting that tDCS has a stronger inhibitory effect on craving for sweet foods than on craving for savoury foods. We have also shown that individuals who exert more

reflective choice behaviours are more susceptible to the anti-craving effects of tDCS than are those who display more impulsive choice behaviours. The potential for DLPFC neuromodulation to transiently alter intertemporal choice behaviour was not supported here and warrants further investigation.

3.6 REFERENCES

Alonso-Alonso, M. & Pascual-Leone, A. (2007). The right brain hypothesis for obesity. *The Journal of the American Medical Association, 297*(16), 1819-1822.

Avena, N. M., Rada, P. & Hoebel, B. G. (2008). Evidence for sugar addiction: Behavioural and neurochemical effects of intermittent, excessive sugar intake. *Neuroscience and Biobehavioural Reviews, 32*(1), 20-29.

Avena, N. M., Rada, P. & Hoebel, B. G. (2009). Sugar and fat bingeing have notable differences in addictive-like behaviour. *The Journal of Nutrition, 139*(3), 623-628.

Blum, K., Liu, Y., Shriner, R., Gold., M. S. (2011). Reward circuitry dopaminergic activation regulates food and drug craving behavior. *Current Pharmaceutical Design, 17*(12), 1158-1167.

Boggio, P. S., Sultani, N., Fecteua, S., Merabet, L., Mecca, T., Pascual-Leone, A… Fregni, F. (2008). Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: A double-blind, sham-controlled study. *Drug and Alcohol Dependence, 92*(1-3), 55-60.

Bonson, K., Grant, S., Comtoreggi, C., Links, J., Metcalfe, J., Weyl., H... London, E. (2002). Neural systems and cue-induced cocaine craving. *Neuropsychopharmacology, 26*(3), 376-386.

Bruinsma, K. & Taren, D. L. (1999). Chocolate: Food or drug? *Journal of the American Dietetic Association, 99*(10), 1249-1256.

Camprodon, J. A., Martinez-Raga, J., Alonso-Alonso, M., Shih, M. C. & Pascual-Leone, A. (2007). One session of high frequency repetitive transcranial magnetic stimulation (rTMS) to the right prefrontal cortex transiently reduces cocaine craving. *Drug and Alcohol Dependence, 86*(1), 91-94.

Cepeda-Benito, A., Gleaves, D. H., Williams, T. L. & Erath, S. A. (2000). The development and validation of the state and trait food craving questionnaires. *Behaviour Therapy, 31*(1), 151-173.

Christakou, A., Brammer, M. & Rubia, K. (2011). Maturation of limbic corticostriatal activation and connectivity associated with developmental changes in temporal discounting. *Neuroimage, 54*(2), 1344-1354.

Clark, L., Manes, F., Antuon, N., Sahakian, B. J. & Robbins, T. W. (2003). The contributions of lesion laterality and lesion volume to decision-making impairment following frontal lobe damage. *Neuropsychologia, 41*(11), 1474-1483.

Cornier, M. A., Salzberg, A. K., Endly, D. C., Bessesen, D. H. & Tregellas, J. R. (2010). Sex-based differences in the behavioural and neural responses to food. *Physiology & Behavior, 99*(4), 538-543.

Davidsen, L., Vistisen, B. & Astrup, A. (2007). Impact of the menstrual cycle on determinants of energy balance: A putative role in weight loss attempts. *International Journal of Obesity, 31*(12), 1777-1785.

Davis, C., Levitan, R. D., Muglia, P., Bewell, C. & Kennedy, J. L. (2004). Decision-making deficits and overeating: A risk model for obesity. *Obesity Research, 12*(6), 929-935.

Davis, C., Patte, K., Curtis, C. & Reid, C. (2010). Immediate pleasures and future consequences: A neurological study of binge eating and obesity. *Appetite, 54*(1), 208-213.

de Wit, H., Flory, J. D., Acheson, A., McCloskey, M. & Manuck, S. B. (2007). IQ and nonplanning impulsivity are independently associated with delay discounting in middle-aged adults. *Personality and Individual Differences, 42*(1), 111-121.

Dom, G., Sabbe, B., Hulstijn, W. & van den Brink, W. (2005). Substance use disorders and the orbitofrontal cortex: Systematic review of behavioural decision-making and neuroimaging studies. *The British Journal of Psychiatry, 187*(3), 209-220.

Downar, J., Sankar, A., Giacobbe, P., Woodside, B. & Colton, P. (2012). Unanticipated rapid remission of refractory bulimia nervosa, during high-dose repetitive transcranial magnetic stimulation of the dorsomedial prefrontal cortex: A case report. *Frontiers in Psychiatry, 3,* 1-5.

Fairburn, C. G., & Beglin, S. J. (1994). Assessment of eating disorders: Interview or self-report questionnaire? *International Journal of Eating Disorders, 16*(4), 363–370.

Figner, B., Knoch, D., Johnson, E. J., Krosch, A. R., Lisanby, S. H., Fehr, E. & Weber, E. U. (2010). Lateral prefrontal cortex and self-control in intertemporal choice. *Nature Neuroscience, 13*(5), 538-539.

First, M. B., Spitzer, R. L., Gibbon, M. & Williams, J. B. (2002). *Structured clinical interview for DSM-IV-TR axis I disorders, research version, non-patient edition (SCID-I/NP).* New York: Biometrics Research.

Franken, I. & Muris, P. (2005). Individual differences in reward sensitivity are related to food craving and relative body weight in healthy women. *Appetite, 45*(2), 198-201.

Fregni, F., Fernanda, O., Pedrosa, W., Fecteau, S., Tome, F., Nitsche, M… Boggio, P. (2008a). Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. *Appetite, 51*(1), 34-41.

Fregni, F., Liguori, P., Fecteau, S., Nitsche, M. A., Pascual-Leone, A. & Boggio, P. S. (2008b). Cortical stimulation of the prefrontal cortex with transcranial direct current stimulation reduces cue-provoked smoking craving: A randomised, sham-controlled study. *The Journal of Clinical Psychiatry, 69*(1), 32-40.

Gandiga, P. C., Hummel, F. C. & Cohen, L. G. (2006). Transcranial DC stimulation (tDCS): A tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical Neurophysiology, 117*(4), 845-850.

Garde, A. H. & Hansen, A. M. (2005). Long-term stability of salivary cortisol. *Scandinavian Journal of Clinical and Laboratory Investigation, 65*(5), 433-436.

Gearhardt, A. N., Yokum, S., Orr, P. T., Stice, E., Corbin, W. R. & Brownell, K. D. (2011). Neural correlates of food addiction. *Archives of General Psychiatry, 68*(8), 1-9.

Goldman, R. L., Borckardt, J. J., Frohman, H. A., O'Neil, P. M., Madan, A., Campbell, L. K… George, M. S. (2011). Prefrontal cortex transcranial direct current stimulation (tDCS) temporarily reduces food cravings and increases the self-reported ability to resist food in adults with frequent food craving. *Appetite, 56*(3), 741-746.

Green, L., Myerson, J., Lichtman, D., Rosen, S. & Fry, A. (1996). Temporal discounting in choice between delayed rewards: The role of age and income. *Psychology and Aging, 11*(1), 79-84.

Grüsser, S. M., Wrase, J., Klein, S., Hermann, D., Smolka, M. N., Ruf, M... Heinz, A. (2004). Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. *Psychopharmacology, 175*(3), 296-302.

Hare, T. A., Camerer, C. F. & Rangel, A. (2009). Self-control in decision-making involves modulation of the vmPFC valuation system. *Science, 324*(5927), 646-648.

Hayashi, T., Ko, J. H., Strafella, A. P. & Dagher, A. (2013). Dorsolateral prefrontal and orbitofrontal cortex interactions during self-control of cigarette craving. *Proceedings of the National Academy of Sciences, 110*(11), 4422-4427.

Hill, A. J. (2007). The psychology of food craving. *Proceedings of the Nutrition Society, 66*(2), 277-285.

Hoogendam, J. M., Ramakers, G. M. & Lazzaro, V. D. (2010). Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimulation, 3*(2), 95-118.

Iyer, M. B., Mattu, U., Grafman, J., Lomarev, M., Sato, S. & Wasserman, E. M. (2005). Safety and cognitive effect of frontal DC brain polarisation in healthy individuals. *Neurology, 64*(5), 872-875.

Jansen, J. M., Daams, J. G., Koeter, M. W., Veltman, D. J., van den Brink, W. & Groudiaan, A. E. (2013). Effects of non-invasive neurostimulation on craving: A meta-analysis. *Neuroscience and Biobehavioral Reviews, 37*(10), 2472-2480.

Kishinevsky, F. I., Cox, J. E., Murdaugh, D. L., Stoeckel, L. E., Cook, E. W. & Weller, R. E. (2012). fMRI reactivity on a delay discounting task predicts weight gain in obese women. *Appetite, 58*(2), 582-592.

Lafay, L., Thomas, F., Mennen, L., Charles, M. A., Eschwege, E., Borys, J. M. & Basdevant, A. (2000). Gender differences in the relation between food cravings and mood in an adult community: Results from the Fleurbaix Laventie Ville Santé study. *International Journal of Eating Disorders, 29*(2), 195-204.

Landis, A. M., Parker, K. P. & Dunbar, S. B. (2009). Sleep, hunger, satiety, food cravings, and caloric intake in adolescents. *Journal of Nursing Scholarship, 41*(2), 115-123.

Li, X., Hartwell, K. J., Owens, M., LeMatty, T., Borckardt, J. J., Hanlon, C. A… George, M. S. (2013). Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex reduces nicotine cue craving. *Biological Psychiatry, 73*(8), 714-720.

Liebetanz, D., Koch, R., Mayenfels, S., König, F., Paulus, W. & Nitsche, M. A. (2009). Safety limits of cathodal transcranial direct current stimulation in rats. *Clinical Neurophysiology, 120*(6), 1161-1167.

Lovibond, S. H. & Lovibond, P. F. (1995). *Manual for the depression anxiety and stress scales* (2nd ed.). Sydney: Psychology Foundation.

Maas, L. C., Lukas, S. E., Kaufman, M. J., Weiss, R. D., Daniels, S. L., Rogers, V. W… Renshaw, P. F. (1998). Functional magnetic resonance imaging of human brain activation during cue-induced cocaine craving. *The American Journal of Psychiatry, 155*(1), 124-126.

Manasse, S. M., Espel, H. M., Schumacher, L. M., Kerrigan, S. G., Zhang, F., Forman, E. M. & Juarascio, A. S. (2016). Does impulsivity predict outcome in treatment for binge eating disorder? A multimodal investigation. *Appetite, 105*, 172-179.

Manwaring, J. L., Green, L., Myerson, J., Strube, M. J. & Wilfley, D. E. (2011). Discounting of various types of rewards by women with and without binge eating disorder: Evidence for general rather than specific differences. *The Psychological Record, 61*(4), 561-582.

McBride, D., Barrett, S. P., Kelly, J. T., Aw, A. & Dagher, A. (2006). Effects of expectancy and abstinence on the neural response to smoking cues in cigarette smokers: An fMRI study. *Neuropsychopharmacology, 31*(12), 2728-2738.

McClelland, J., Bozhilova, N., Campbell, I. & Schmidt, U. (2013a). 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.

McClelland, J., Bozhilova, N., Nestler, S., Campbell, I., Jacob, S., Johnson-Sabine, E. & Schmidt, U. (2013b). Improvements in symptoms following neuronavigated repetitive transcranial magnetic stimulation (rTMS) in severe and enduring

anorexia nervosa: Findings from two case studies. *European Eating Disorders Review, 21*(6), 500-506.

Medeiros, L. F., de Souza, I. C., Vidor, L. P., de Souza, A., Deitos, A., Volz, M.S… Torres, I. L. (2012). Neurobiological effects of transcranial direct current stimulation: A review. *Frontiers in Psychiatry, 3,* 1-11.

Meule, A., Westenhöfer, J. & Kübler, A. (2011). Food cravings mediate the relationship between rigid, but not flexible control of eating behavior and dieting success. *Appetite, 57*(3), 582-584.

Mishra, B. R., Nizamie, S. H., Das, B. & Praharaj, S. K. (2010). Efficacy of repetitive transcranial magnetic stimulation in alcohol dependence: A sham-controlled study. *Addiction, 105*(1), 49-55.

National Health Service (NHS). (2012). *What's your BMI?* Retrieved from http://www.nhs.uk/Live well/loseweight/Pages/BodyMassIndex.aspx

National Health Service (NHS). (2013). *Alcohol Units*. Retrieved from http://www.nhs.uk/Livewell /alcohol/Pages/alcohol-units.aspx

Ng, L. & Davis, C. (2013). Cravings and food consumption in binge eating disorder. *Eating Behaviors, 14*(4), 472-475.

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A… Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation, 1*(3), 206-223.

Nitsche, M. A. & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology, 57*(10), 1899-1901.

Odom, J., Zalesin, K. C., Washington, T. L., Miller, W. W., Hakmeh, B., Zaremba, D. L… McCullough, P. A. (2010). Behavioural predictors of weight regain after bariatric surgery. *Obesity Surgery, 20*(3), 349-356.

Pelchat, M. L. (2009). Food addiction in humans. *The Journal of Nutrition, 139*(3), 620-622.

Pelchat, M. L. (2002). Of human bondage: Food craving, obsession, compulsion, and addiction. *Physiology & Behavior, 76*(3), 347-352.

Pelchat, M. L., Johnson, A., Chan, R., Valdez, J. & Ragland, D. (2004). Images of desire: Food-craving activation during fMRI. *NeuroImage, 23*(4), 1486-1493.

Politi, E., Fauci, E., Santoro, A. & Smeraldi, E. (2008). Daily sessions of transcranial magnetic stimulation to the left prefrontal cortex gradually reduce cocaine craving. *The American Journal on Addictions, 17*(4), 345-346.

Poll, E. M., Kreitschmann-Andermahr, I., Langejuergen, Y., Stanzel, S., Gilsbach, J. M., Gressner, A. & Yagmur, E. (2007). Saliva collection method affects predictability of serum cortisol. *Clinica Chimica Acta, 382*(1-2), 15-19.

Poreisz, C., Boros, K., Antal, A. & Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Research Bulletin, 72*(4-6), 208-214.

Priori, A., Hallett, M. & Rothwell, J. C. (2009). Repetitive transcranial magnetic stimulation or transcranial direct current stimulation? *Brain Stimulation, 2*(4), 241-245.

Rachlin, H., Raineri, A. & Cross, D. (1991). Subjective probability and delay. *Journal of the Experimental Analysis of Behavior, 55*(2), 233-244.

Richards, J. B., Zhang, L., Mitchell, S. H. & de Wit, H. (1999). Delay or probability discounting in a model of impulsive behaviour: Effect of alcohol. *Journal of the Experimental Analysis of Behaviour, 71*(2), 121-143.

Rø, Ø., Reas, D. L. & Rosenvinge, J. (2012). The impact of age and BMI on Eating Disorder Examination Questionnaire (EDE-Q) scores in a community sample. *Eating Behaviours, 13*(2), 158-161.

Rosenberg, H. (2009). Clinical and laboratory assessment of the subjective experience of drug craving. *Clinical Psychology Review, 29*(6), 519-534.

Rubia, K., Halari, R., Christakou, A. & Taylor, E. (2009). Impulsiveness as a timing disturbance: neurocognitive abnormalities in attention-deficit hyperactivity disorder during temporal processes and normalisation with methylphenidate. *Philosophical Transactions of the Royal Society, 364*(1525), 1919-1931.

Schienle, A., Schäfer, A., Hermann, A. & Vaitl, D. (2009). Binge-eating disorder: Reward sensitivity and brain activation to images of food. *Biological Psychiatry, 65*(8), 654-661.

Siep, N., Roefs, A., Roebroeck, A., Havemans, R., Bonte, M. & Jansen, A. (2009). Hunger is the best spice: An fMRI study of the effects of attention, hunger and calorie content on food reward processing in the amygdala and orbitofrontal cortex. *Behavioural Brain Research, 198*(1), 149-158.

Steinglass, J. E., Figner, B., Berkowitz, S., Simpson, H. B., Weber, E. U., & Walsh, B. T. (2012). Increased capacity to delay reward in anorexia nervosa. *Journal of the International Neuropsychological Society*, *18*(4), 773-780.

Tang, D. W., Fellows, L. K., Small, D. M., Dagher, A. (2012). Food and drug cues activate similar brain regions: A meta-analysis of functional MRI studies. *Physiology & Behavior, 106*(3), 317-324.

Uher, R., Yoganathan, D., Mogg, A., Eranti, S. V., Treasure, J., Campbell, I. C…& Schmidt, U. (2005). Effect of left prefrontal repetitive transcranial magnetic stimulation on food craving. *Biological Psychiatry, 58*(10), 840-842.

Van den Eynde, F., Claudino, A. M., Mogg, A., Horrell, L., Stahl, D., Ribeiro, W… Schmidt, U. (2010). Repetitive transcranial magnetic stimulation reduces cue-induced food craving in bulimic disorders. *Biological Psychiatry, 67*(8), 793-795.

Van den Eynde, F., Guillaume, S., Broadbent, H., Campbell, I. & Schmidt, U. (2013). Repetitive transcranial magnetic stimulation in anorexia nervosa: A pilot study. *European Psychiatry, 28*(2), 98-101.

Volkow, N. D. & Wise, R. A. (2005). How can drug addiction help us understand obesity? *Nature Neuroscience, 8*(5), 555-560.

Weller, R. E., Cook III, E. W., Avsar, K. B. & Cox, J. E. (2008). Obese women show greater delay discounting than healthy-weight women. *Appetite, 51*(3), 563-569.

Wexler, B. E., Gottschalk, C. H., Fulbright, R. K., Prohovnik, I., Lacadie, C. M., Rounsaville, B. J. & Gore, J. C. (2001). Functional magnetic resonance imaging of cocaine craving. *The American Journal of Psychiatry, 158*(1), 86-95.

Yalachkov, Y., Kaiser, J. & Naumer, M. J. (2009). Brain regions related to tool use and action knowledge reflect nicotine dependence. *The Journal of Neuroscience, 29*(15), 4922-4929.

Yanovski, S. (2003). Sugar and fat: Cravings and aversions. *The Journal of Nutrition, 133*(3), 835-837.

Chapter 4. Increased temporal discounting in bulimia nervosa

Kekic, M*., Bartholdy, S*., Cheng, J., McClelland, J., Boysen, E., Musiat, P.,… Schmidt, U. (2016). Increased temporal discounting in bulimia nervosa. *International Journal of Eating Disorders, 49,* 1077-1081.

* Joint first authorship.

4.1 ABSTRACT

Objective: There is evidence that people with eating disorders display altered intertemporal choice behaviour (the degree of preference for immediate rewards over delayed rewards). Compared to healthy controls (HC), individuals with anorexia nervosa and binge-eating disorder show decreased and increased rates of temporal discounting (TD; the devaluation of delayed rewards), respectively. This is the first study to investigate TD in people with bulimia nervosa (BN).

Method: Thirty-nine individuals with BN (2 men) and 53 HC (9 men) completed a hypothetical monetary TD task. Over 80 binary choices, participants chose whether they would prefer to receive a smaller amount of money available immediately or a larger amount available in 3 months. Self-reported ability to delay gratification (the behavioural opposite of TD) was also measured.

Results: Individuals with BN showed greater TD (i.e., a preference for smaller-sooner rewards) and a decreased self-reported capacity to delay gratification relative to HC. Experimental groups did not differ in age, gender ratio, or BMI.

Discussion: Increased rates of TD may contribute to some of the core symptoms of BN that appear to involve making choices between immediate and delayed rewards (i.e., binge-eating and compensatory behaviours). Altered intertemporal choice behaviour could therefore be a relevant target for intervention in this patient group.

4.2 INTRODUCTION

The pathophysiology of bulimia nervosa (BN) is poorly understood and strong evidence to guide treatment is lacking (Guillaume et al., 2010). Exploration of neurocognition in BN has the potential to elucidate mechanisms underpinning associated behavioural abnormalities, and to promote the development of tailored therapeutic interventions.

Several neuropsychological difficulties have been observed in BN (Van den Eynde et al., 2011). For example, individuals with BN, as well as other eating disorders (EDs; anorexia nervosa [AN] and binge-eating disorder [BED]), have an increased preference for risky and disadvantageous choices in a context of uncertainty (Guillaume et al., 2015). There is also evidence that patients with EDs make maladaptive intertemporal choices. A reward arriving sooner is often more appealing than one arriving later, even when the later reward is larger. Thus, individuals discount the value of delayed outcomes – a phenomenon known as temporal discounting (TD). This tendency to devalue future rewards appears to be accentuated in BED (increased TD) (Mole et al., 2015) and diminished in AN (decreased TD) (Steinglass et al., 2012), which may underlie the disinhibited and restrictive eating that characterise these disorders. This study investigated whether individuals with BN display altered rates of TD and differences in the self-reported capacity to delay gratification relative to healthy controls (HC).

4.3 MATERIAL AND METHODS

4.3.1 Participants

Participants were men and women ≥18 years with BN or no current/previous diagnosis of any psychiatric disorder (HC): their data were pooled from two larger studies conducted by our group (currently in preparation for publication). Patients with BN were

recruited via online advertisements on the King's College London (KCL) and Beat™ research recruitment webpages and through the South London and Maudsley NHS Foundation Trust ED Outpatient Service, while HC responded to online and poster advertisements at KCL. Group classification was established via self-report and checked over email/telephone: *DSM-5* BN diagnosis was confirmed using an edited version of the Eating Disorder Diagnostic Scale (EDDS) (Stice, Telch, & Rizvi, 2000), and the absence of a psychiatric disorder in HC was confirmed using the EDDS and the Structured Clinical Interview for *DSM-IV* Axis I Disorders Screening Module (First, Spitzer, Gibbon, & Williams, 2002).

One hundred and thirty participants (BN = 55; HC = 75) completed the screening and 122 (BN = 52; HC = 70) were eligible for inclusion. Of these, 92 (BN = 39; HC = 53) completed the study and were included in the analyses.

The two larger studies were approved by the KCL Psychiatry, Nursing and Midwifery Research Ethics Subcommittee and the London City Road & Hampstead Research Ethics Committee. Participants gave informed consent prior to taking part and were compensated for their time.

4.3.2 Procedure

All participants attended a testing session at the Institute of Psychiatry, Psychology & Neuroscience, KCL. Study procedures undertaken prior to the TD task were comparable between the two studies (Figures 4.1 and 4.2): both involved providing written consent and completing several identical questionnaires, including the Depression Anxiety and Stress Scales (DASS-21) (Lovibond & Lovibond, 1995) and the Delaying Gratification Inventory (DGI) (Hoerger, Quirk, & Weed, 2011). Additionally, in both cases the TD

task was done on a laptop with an experimenter present. Data were collected between May 2014 and September 2015.

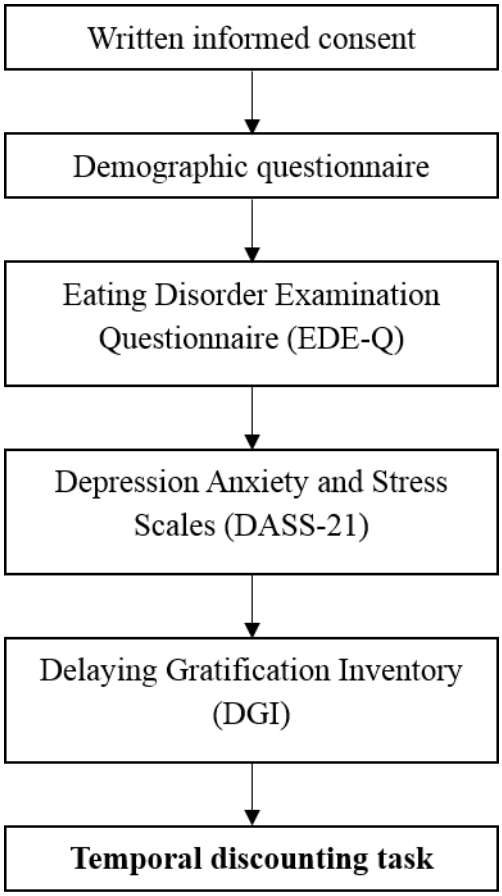


Figure 4.1 Flow chart showing the measures completed prior to the temporal discounting task in Study 1 ("Transcranial direct current stimulation improves symptoms, mood, and self-regulatory control in bulimia nervosa: A randomised controlled trial").

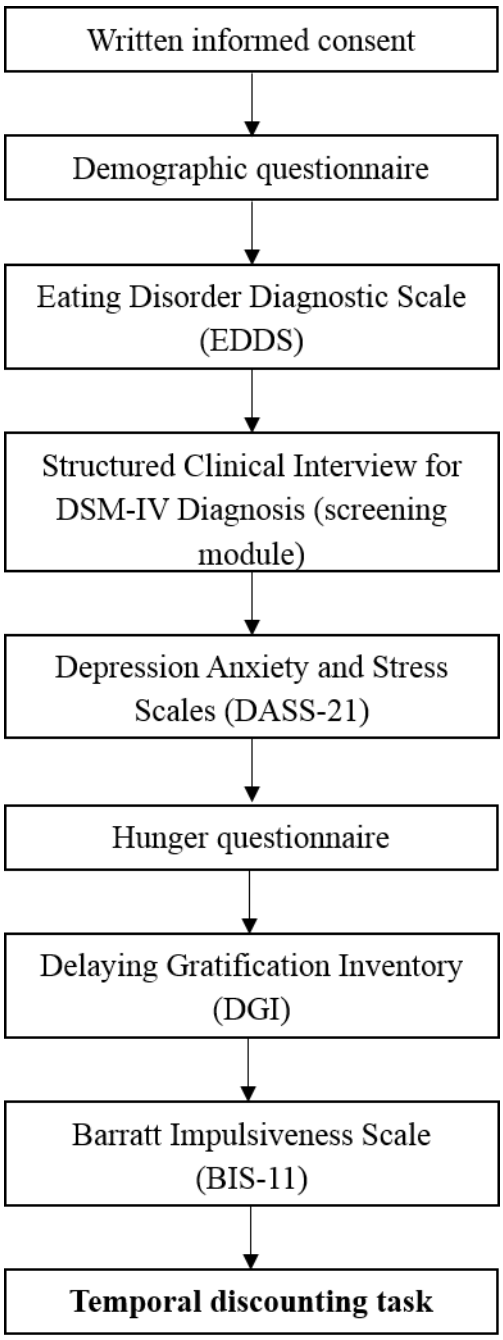


Figure 4.2 Flow chart showing the measures completed prior to the temporal discounting task in Study 2 ("The impact of acute food restriction and distractor relevance on inhibitory control in healthy adults").

4.3.3 Further description of the two larger studies

The two studies had unrelated aims: Study 1 was a crossover randomised controlled trial assessing the effects of transcranial direct current stimulation (tDCS) in bulimia

nervosa, and Study 2 explored the impact of acute food restriction and distractor relevance on inhibitory control in healthy controls. Whereas these studies assessed within-subject differences in temporal discounting due to tDCS treatment and acute fasting, respectively, the present research combined their baseline temporal discounting and delaying gratification data to evaluate between-group differences in intertemporal choice behaviour.

4.3.4 Temporal discounting task

TD was assessed using a computerised hypothetical monetary choice task, modelled on an established paradigm[11] (Steinglass et al., 2012). On each of 80 trials, participants had an unrestricted amount of time to indicate whether they would prefer to receive a smaller amount of money immediately (smaller-sooner reward) or a larger amount after 3 months (larger-later reward). Two types of decision framing were employed: 'Accelerate' (larger-later reward remained at £100, smaller-sooner reward increased from £20 to £98 in £2 increments) and 'Delay' (smaller-sooner reward remained at £50, larger-later reward increased from £52 to £130 in £2 increments) (40 trials for each). The trials were pseudo-randomly interleaved, so that the two decision frames were intermixed.

TD was quantified by determining participants' discount factor (DF) – the magnitude of reduction in the present value of a future reward – for each choice set using a two-step procedure (Steinglass et al., 2012). First, the 'indifference point' was established. This is

[11] It was suspected that the TD task employed in the study presented in chapter 3 lacked sensitivity due to the sole use of 'Accelerate' decision framing (see section 3.5). A novel TD task containing both 'Accelerate' and 'Delay' framing was therefore developed by our team for use in this study and in the study presented in chapter 5.

the amount of money that the participant judged as equivalent to the fixed reward – i.e., the value of the variable reward when the participant switched from larger-later to smaller-sooner in the Accelerate set and from smaller-sooner to larger-later in the Delay set (Steinglass et al., 2012). Second, a mathematical formula was fitted to the indifference point: $\delta = (x_1/x_2)^{(1/(t2-t1))}$, where x_1 is the smaller-sooner reward, x_2 is the larger-later reward, and t_2-t_1 is the delay to reward presentation (in years), which in this case was 0.25 (Steinglass et al., 2012; Weber et al., 2007). This procedure is a sensitive measure of temporal discounting that is independent of hyperbolic modelling and area under the curve analyses (Steinglass et al., 2012; Weber et al., 2007). Global DF was calculated as the mean of the two DFs, and was used as the primary outcome variable in this study. The value obtained can range from 0 to 1, with smaller numbers indicating greater TD (i.e., a greater tendency to choose the smaller-sooner reward).

4.3.5 Delaying Gratification Inventory

Self-reported ability to delay gratification was measured with the DGI, which requires respondents to rate the extent to which they agree with 35 statements on a 5-point Likert scale. Scores are generated for five domains of delay behaviour (Food, Physical Pleasures, Social Interactions, Money, and Achievement) and a total score (Global DGI score) is calculated. This was used as the outcome variable here. Higher values indicate a greater capacity to delay gratification.

4.3 RESULTS

Statistical analyses were performed using SPSS® (tests were two-tailed, $\alpha = 0.05$). Key sample characteristics and raw intertemporal choice data are provided in Table 4.1. TD data were positively skewed, therefore square-root transformations were applied and

transformed values were used in all subsequent analyses. Global DFs and Global DGI scores were correlated in the sample as a whole [r = 0.33, p = .002] (i.e., the higher the rate of TD, the lower the ability to delay gratification).

Table 4.1 Sample characteristics and raw intertemporal choice data.

	HC (n = 53)		BN (n = 39)		
	M [n]	SD [%]	M [n]	SD [%]	p
Age	25.55	7.33	25.85	6.62	.442[c]
Gender	-	-	-	-	.083[d]
Female	[44]	[83.02]	[37]	[94.87]	-
Male	[9]	[16.98]	[2]	[5.13]	-
BMI[a]	21.71	2.17	21.65	3.20	.420[c]
DASS-21 depression	2.68	2.96	20.62	10.39	< .000[c]
DASS-21 anxiety	2.57	3.60	15.23	11.65	< .000[c]
DASS-21 stress	6.64	5.24	21.97	10.19	< .000[e]
EDE-Q global	-	-	4.21	1.06	-
Illness duration (months)	-	-	110.87	95.62	-
Binge-eating frequency[b]	-	-	22.23	31.66	-
Vomiting frequency[b]	-	-	50.87	169.5	-
Laxative use frequency[b]	-	-	4.69	17.28	-
Excessive exercise frequency[b]	-	-	7.21	9.99	-
DF Accelerate	0.45	0.35	0.32	0.34	.046[c]
DF Delay	0.42	0.31	0.27	0.04	.012[c]
DF Global	0.44	0.31	0.30	0.29	.020[c]

DGI global	140.79	12.86	121.85	15.24	< .000[e]

HC, healthy controls; BN, bulimia nervosa; DF, discount factor (from temporal discounting task); DGI, Delaying Gratification Inventory; M, mean; SD, standard deviation; BMI, body mass index.

[a] weight(kg)/(height(m))^2

[b] Number of times in the previous 28 days

[c] Mann-Whitney *U* test

[d] Pearson chi-squared test

[e] Independent samples *t*-test

A one-way multivariate ANOVA showed that individuals with BN had lower Global DFs (indicating an increased rate of TD) [$F(1, 90) = 5.72$, $p = .019$] and Global DGI scores (indicating a reduced capacity to delay gratification) [$F(1, 90) = 41.65$, $p < .001$] than HC. To examine whether these group differences persisted after controlling for other possible determinants, age, gender, BMI, and DASS-21 depression, anxiety, and stress scores were entered into the model as covariates. This revealed a significant effect of group on Global DF [$F(1, 84) = 5.52$, $p = .021$] but not Global DGI score [$F(1, 84) = 2.24$, $p = .138$], due to the inclusion of DASS-21 stress scores [$F(1, 84) = 5.25$, $p = .024$]. An exploratory mixed ANOVA revealed no significant main effect of framing (Accelerate vs. Delay) or framing x group interaction on DFs [both $p \geq .654$].

Bivariate correlations were used to explore relationships between Global DFs, Global DGI scores, clinical outcomes (DASS-21 and EDE-Q scores, illness duration, and frequency of binge-eating, vomiting, laxative use, and excessive exercise), and BMI. Pearson's r and Spearman's rho correlation coefficients were employed. In the BN group, Global DFs were not significantly related to any clinical variables [all $p > .109$], and Global DGI scores were also not significantly correlated with any clinical variables [all $p \geq .278$] except for DASS-21 depression [$r = -0.34$, $p = .036$] and stress [$r = -0.39$, $p =$

.013] scores. Neither Global DFs nor Global DGI scores were associated with BMI when the BN and HC groups were considered separately or together [all $p \geq .233$].

4.4 DISCUSSION

This is the first study to assess intertemporal choice behaviour in BN. Individuals with BN displayed steeper rates of TD (i.e., an increased preference for smaller-sooner rewards) and a reduced self-reported capacity to delay gratification compared to HC. This is consistent with observations of disadvantageous monetary decision-making in BN (Guillaume et al., 2015) and with TD findings in BED (Mole et al., 2015), but contrasts with the lower rates of TD reported in AN (which reflect an increased preference for larger-later rewards) (Steinglass et al., 2012).

Group differences in TD remained significant after controlling for variables reported to influence discounting rates (age, gender, BMI, depression, anxiety, and stress). TD did not correlate with illness duration, symptom severity, general psychopathology, or BMI among individuals with BN, suggesting that elevated TD reflects a stable neurocognitive feature of BN. It may also be that our sample was too small or had insufficient variability to detect what might have been a weak correlation between TD and clinical variables. Indeed, unpublished data from our team demonstrate weak but significant correlations between TD and binge-eating among 432 participants with or without a clinical eating disorder. As our study only included acutely ill individuals, we cannot determine whether TD is a trait- or state-based marker of illness. Interestingly, a recent study reported that reduced TD in AN normalised after weight restoration (Decker, Figner, & Steinglass, 2015); thus, studies should explore whether increased TD in BN persists after recovery.

In contrast to TD rates, group differences in DGI scores disappeared after controlling for stress, and a decreased self-reported capacity to delay reward was associated with greater stress and depression in the BN group. Stress may therefore influence the perception of one's tendencies to delay gratification, but not the behaviour itself. We did not replicate the finding that people discount future rewards more when they are asked to delay consumption than when they are offered the chance to accelerate consumption (Steinglass et al., 2012; Weber et al., 2007), which may be due to differences in the TD task administered.

A reduced capacity to delay reward may underpin some of the core symptoms of BN. For example, greater TD is proposed to reflect choice impulsivity and poor reward-related inhibitory control (Bari & Robbins, 2013), and these neurocognitive difficulties are implicated in binge-eating and compensatory behaviours. Furthermore, binge-eating can be regarded as a manifestation of the tendency to act in pursuit of immediate pleasure-driven desires, as people with BN have heightened reward sensitivity to food cues (Brooks et al., 2011) and report that binge-eating relieves negative affect (De Young, Zander, & Anderson, 2014). Altered intertemporal choice behaviour could therefore be a relevant target for intervention in this patient group.

Excessive TD is not exclusive to BN and BED: it relates to a broader set of psychiatric conditions, including addictions and schizophrenia, and to a number of behavioural maladies, such as unsafe sex and poor health practices (Bickel, Jarmolowicz, Mueller, Koffarnus, & Gatchalian, 2012). It has therefore been proposed to function as a trans-disease process, potentially underscored by a neurobiological imbalance between the 'impulsive' and 'executive' decision systems, which are embodied in parts of the limbic/paralimbic brain regions and prefrontal cortices, respectively (Bickel et al.,

2012). In this view, effective interventions will be those that restore regulatory balance to these competing systems (Koffarnus, Jarmolowicz, Mueller, & Bickel, 2013). Indeed, we recently found that direct manipulation of the executive system with transcranial magnetic stimulation concurrently altered TD and improved symptoms in AN (McClelland et al., 2016).

This study has some limitations. Firstly, most participants were women, which may have introduced a gender bias (Weller, Cook, Avsar, & Cox, 2008); however, the male-to-female ratio did not differ between groups and a predominantly female sample reflects the higher prevalence of BN in women than in men. Secondly, we were unable to explore between-group differences in income, education, or IQ, which may influence the subjective evaluation of monetary rewards (de Wit, Flory, Acheson, McCloskey, & Manuck, 2007; Green, Myerson, Lichtman, Rosen, & Fry, 1996). Finally, although the paradigm included more trials than most TD tasks, our findings are restricted to choices between immediate rewards and those delayed by three months: future studies should confirm the results using multiple time-points, permitting hyperbolic modelling of discounting.

4.5 REFERENCES

Bari, A., & Robbins, T. W. (2013). Inhibition and impulsivity: Behavioral and neural basis of response control. *Progress in Neurobiology, 108*, 44-79.

Bickel, W. K., Jarmolowicz, D. P., Mueller, E. T., Koffarnus, M. N., & Gatchalian, K. M. (2012). Excessive discounting of delayed reinforcers as a trans-disease process contributing to addiction and other disease-related vulnerabilities: Emerging evidence. *Pharmacology and Therapeutics, 134*(3), 287-297.

Brooks, S. J., O'Daly, O. G., Uher, R., Friederich, H. C., Giampietro, V., Brammer, M., . . . Campbell, I. C. (2011). Differential neural responses to food images in women with bulimia versus anorexia nervosa. *PLOS ONE, 6*(7).

de Wit, H., Flory, J. D., Acheson, A., McCloskey, M., & Manuck, S. B. (2007). IQ and nonplanning impulsivity are independently associated with delay discounting in middle-aged adults. *Personality and Individual Differences, 42*(1), 111-121.

De Young, K. P., Zander, M., & Anderson, D. A. (2014). Beliefs about the emotional consequences of eating and binge eating frequency. *Eating Behaviors, 15*(1), 31-36.

Decker, J. H., Figner, B., & Steinglass, J. E. (2015). On Weight and Waiting: Delay Discounting in Anorexia Nervosa Pretreatment and Posttreatment. *Biological Psychiatry, 78*(9), 606-614.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (2002). *Structured clinical interview for DSM-IV-TR axis I disorders, research version, non-patient edition (SCID-I/NP)*. New York: Biometrics Research.

Green, L., Myerson, J., Lichtman, D., Rosen, S., & Fry, A. (1996). Temporal discounting in choice between delayed rewards: the role of age and income. *Psychology and Aging, 11*(1), 79.

Guillaume, S., Gorwood, P., Jollant, F., Van den Eynde, F., Courtet, P., & Richard-Devantoy, S. (2015). Impaired decision-making in symptomatic anorexia and bulimia nervosa patients: A meta-analysis. *Psychological Medicine, 45*(16), 3377-3391.

Guillaume, S., Sang, C. N. T., Jaussent, I., Raingeard, I., Bringer, J., Jollant, F., & Courtet, P. (2010). Is decision making really impaired in eating disorders? *Neuropsychology, 24*(6), 808-812.

Hoerger, M., Quirk, S. W., & Weed, N. C. (2011). Development and validation of the Delaying Gratification Inventory. *Psychological Assessment, 23*(3), 725-738.

Koffarnus, M. N., Jarmolowicz, D. P., Mueller, E. T., & Bickel, W. K. (2013). Changing delay discounting in the light of the competing neurobehavioral decision systems theory: A review. *Journal of the Experimental Analysis of Behavior, 99*(1), 32-57.

Lovibond, S. H., & Lovibond, P. F. (1995). *Manual for the Depression Anxiety Stress Scales* (2nd ed.). Sydney: Psychology Foundation.

McClelland, J., Kekic, M., Bozhilova, N., Nestler, S., Dew, T., Van den Eynde, F., . . . Schmidt, U. (2016). A randomised controlled trial of neuronavigated repetitive transcranial magnetic stimulation (rTMS) in anorexia nervosa. *PLOS ONE, 11*(3).

Mole, T. B., Irvine, M. A., Worbe, Y., Collins, P., Mitchell, S. P., Bolton, S., . . . Voon, V. (2015). Impulsivity in disorders of food and drug misuse. *Psychological Medicine, 45*(4), 771-782.

Steinglass, J. E., Figner, B., Berkowitz, S., Simpson, H. B., Weber, E. U., & Walsh, B. T. (2012). Increased capacity to delay reward in anorexia nervosa. *Journal of the International Neuropsychological Society, 18*(04), 773-780.

Stice, E., Telch, C. F., & Rizvi, S. L. (2000). Development and validation of the Eating Disorder Diagnostic Scale: A brief self-report measure of anorexia, bulimia, and binge-eating disorder. *Psychological Assessment, 12*(2), 123-131.

Van den Eynde, F., Guillaume, S., Broadbent, H., Stahl, D., Campbell, I., Schmidt, U., & Tchanturia, K. (2011). Neurocognition in bulimic eating disorders: A systematic review. *Acta Psychiatrica Scandinavica, 124*(2), 120-140.

Weber, E. U., Johnson, E. J., Milch, K. F., Chang, H., Brodscholl, J. C., & Goldstein, D. G. (2007). Asymmetric discounting in intertemporal choice: A query-theory account. *Psychological Science, 18*(6), 516-523.

Weller, R. E., Cook, E. W., 3rd, Avsar, K. B., & Cox, J. E. (2008). Obese women show greater delay discounting than healthy-weight women. *Appetite, 51*(3), 563-569.

Chapter 5. Transcranial direct current stimulation improves symptoms, mood, and self-regulatory control in bulimia nervosa: A randomised controlled trial

---

Kekic, M., McClelland, J., Bartholdy, S., Boysen, E., Musiat, P., Dalton, B.,… Schmidt, U. (2017). Transcranial direct current stimulation improves symptoms, mood, and self-regulatory control in bulimia nervosa: A randomised controlled trial. *PLOS ONE, 12*(1).

5.1 ABSTRACT

Background: Evidence suggests that pathological eating behaviours in bulimia nervosa (BN) are underpinned by alterations in reward processing and self-regulatory control, and by functional changes in neurocircuitry encompassing the dorsolateral prefrontal cortex (DLPFC). Manipulation of this region with transcranial direct current stimulation (tDCS) may therefore alleviate symptoms of the disorder.

Objective: This double-blind sham-controlled proof-of-principle trial investigated the effects of bilateral tDCS over the DLPFC in adults with BN.

Methods: Thirty-nine participants (two males) received three sessions of tDCS in a randomised and counterbalanced order: anode right/cathode left (AR/CL), anode left/cathode right (AL/CR), and sham. A battery of psychological/neurocognitive measures was completed before and after each session and the frequency of bulimic behaviours during the following 24-hours was recorded.

Results: AR/CL tDCS reduced eating disorder cognitions (indexed by the Mizes Eating Disorder Cognitions Questionnaire-Revised) when compared to AL/CR and sham tDCS. Both active conditions suppressed the self-reported urge to binge-eat and increased self-regulatory control during a temporal discounting task. Compared to sham stimulation, mood (assessed with the Profile of Mood States) improved after AR/CL but not AL/CR tDCS. Lastly, the three tDCS sessions had comparable effects on the wanting/liking of food and on bulimic behaviours during the 24 hours post-stimulation.

Conclusions: These data suggest that single-session tDCS transiently improves symptoms of BN. They also help to elucidate possible mechanisms of action and highlight the importance of selecting the optimal electrode montage. Multi-session trials are needed to determine whether tDCS has potential for development as a treatment for adult BN.

5.2 INTRODUCTION

Bulimia nervosa (BN) is characterised by recurrent episodes of binge-eating and inappropriate compensatory behaviours. It typically emerges during adolescence and is associated with substantial functional impairment, suicidality (Stice, Marti, & Rohde, 2013), and an increased risk of mortality (Arcelus, Mitchell, Wales, & Nielsen, 2011; Smink, van Hoeken, & Hoek, 2012). Furthermore, BN has high rates of comorbidity with major mood, anxiety, impulse control, and substance use disorders (Hudson, Hiripi, Pope Jr, & Kessler, 2007). Lifetime prevalence estimates for young women are 7% when subthreshold cases are considered (Stice et al., 2013). Cognitive behavioural therapy is regarded as the gold-standard treatment (National Institute for Health and Care Excellence, 2004), yet most patients remain symptomatic following therapy (Poulsen et al., 2014) and attrition rates are as high as 50% (Penas-Lledo et al., 2013).

Development of novel therapies for BN relies on identifying factors that contribute to pathogenesis. Evidence indicates that alterations in reward processing may play a central role; for example, patients with BN rate pictures of food as more interesting/arousing than healthy controls (Mauler, Hamm, Weike, & Tuschen-Caffier, 2006) and bulimic symptoms correlate positively with reward sensitivity (Farmer, Nash, & Field, 2001; Loxton & Dawe, 2001). Neuroimaging data support the importance of reward systems in BN: both hyper- and hypo-responsivity have been observed in the neural networks that subserve anticipatory (wanting) and consummatory (liking) food reward processing (Friederich, Wu, Simon, & Herzog, 2013; Garcia-Garcia et al., 2013; Wierenga et al., 2014). Individuals with BN also appear to have deficient self-regulatory control, thus increasing instability and erratic responding to rewarding stimuli (Wierenga et al., 2014). For example, BN (Wu et al., 2016) and binge-eating more generally (Bartholdy, Dalton, O'Daly, Campbell, & Schmidt, 2016) are associated with

impaired reactive response inhibition, and our group recently observed an increased propensity to devalue delayed rewards (a concept known as temporal discounting; TD) in patients with BN relative to healthy controls (Kekic et al., 2016a). Neuroimaging studies suggest these difficulties are related to hypoactivity in circuitry that supports self-regulatory capacities (Marsh et al., 2011; Marsh et al., 2009). It has therefore been proposed that disturbed eating in BN is underpinned by problems in reward processing and self-regulatory control, which correspond to aberrations within ventral limbic and dorsal cognitive frontostriatal neural networks, respectively (Berner & Marsh, 2014; Friederich et al., 2013; Wierenga et al., 2014). Negative mood may trigger binge-eating by altering the reward value of food (Bohon & Stice, 2012; Wagner, Boswell, Kelley, & Heatherton, 2012) and by diminishing self-regulatory processes (Heatherton & Wagner, 2011).

Non-invasive brain stimulation (NIBS) enables targeted manipulation of cortical excitability, and may be useful for 'normalising' altered neural circuit activity in BN. The most common NIBS modalities are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). rTMS uses a coil to generate a magnetic field, which penetrates the skull and induces an electrical current, whereas tDCS delivers a low-amplitude direct current via two surface electrodes (anode and cathode). Although both methods are well-tolerated and have minimal side effects, tDCS has several practical advantages over rTMS: it is portable, inexpensive, has a more favourable safety-feasibility profile, and can be applied bilaterally.

Evidence for the usefulness of NIBS in psychiatry is accumulating, and the dorsolateral prefrontal cortex (DLPFC) has been the targeted site in most studies. This region is part of the dorsal cognitive frontostriatal circuitry – representing the major neural structure

involved in executive functions, including self-regulatory control (Hare, Camerer, & Rangel, 2009) – and is also implicated in reward processing due to its anatomical/functional connections with ventral limbic circuitry (Diana, 2011). Given the aetiological relevance of these neurocognitive capacities in BN, manipulating the DLPFC with NIBS might alleviate symptoms of the disorder (McClelland, Bozhilova, Campbell, & Schmidt, 2013). Indeed, our group found that one session of real versus sham rTMS over the left DLPFC was associated with a decreased urge to eat and fewer binge-eating episodes during the 24-hour follow-up period in 38 participants with a bulimic disorder (Van den Eynde et al., 2010), and Hausmann et al. (2004) observed complete remission of binge/purge symptoms following 10 sessions of left DLPFC rTMS in a patient with refractory BN. Modulation of the DLPFC with tDCS has produced therapeutic effects in food cravers (Kekic et al., 2014), obese individuals (Gluck et al., 2015), and patients with various psychiatric disorders including anorexia nervosa and binge-eating disorder (Burgess et al., 2016; Kekic, Boysen, Campbell, & Schmidt, 2016b; Khedr, Elfetoh, Ali, & Noamany, 2014); however, its utility in BN has not been explored.

This proof-of-principle clinical trial investigated the effects of two single sessions of sham-controlled tDCS administered bilaterally over the DLPFC (anode right/cathode left [AR/CL] and anode left/cathode right [AL/CR]) in patients with BN. The aims were to establish whether these sessions would temporarily: (i) suppress core symptoms of BN (urge to binge-eat, eating disorder [ED]-related cognitions, frequency of binge-eating and compensatory behaviours); (ii) reduce TD behaviour (an indicator of poor self-regulatory control); (iii) alter the wanting/liking of high- and low-calorie sweet and savoury foods (anticipatory/consummatory reward processing); and (iv) improve mood.

5.3 MATERIAL AND METHODS

5.3.1 Participants

Male and female volunteers (≥ 18 years) with BN were recruited from the King's College London, Beat, Call for Participants, and Experimatch websites, and from the South London and Maudsley NHS Foundation Trust ED outpatient service.[12] Respondents were screened by phone and a *DSM-5* diagnosis of BN was confirmed with an adapted version of the Eating Disorder Diagnostic Scale (EDDS; Stice, Telch, & Rizvi, 2000). Exclusion criteria were: (i) contraindications to tDCS (Brunoni et al., 2012; details available on request); (ii) significant health problems in the previous six months; and (iii) pregnancy. Ongoing parallel treatment was permitted since inter-session intervals were short (M = 9.10 days, SD = 9.39 days) and each participant served as their own control. Fifty-seven people (4 males) completed the telephone screen and 53 fulfilled the eligibility criteria (Figure 5.1). Of these, 39 (2 males) completed all 3 study sessions (the dropout rate was 0%) and 35 (2 males) completed all 3 follow-up questionnaires.

The study was conducted at the Institute of Psychiatry, Psychology & Neuroscience (London, UK). Ethical approval was obtained from the London City Road & Hampstead National Research Ethics Service committee (10th February 2014, 14/LO/0025). All participants provided written informed consent and were debriefed at

[12] A two-way 2 x 3 repeated measures ANOVA sample size calculation (incorporating interaction effects) was conducted using G*Power, with a two-sided significance of 0.05 and a power of 0.95 (number of groups = 3; number of measurements = 6). This indicated that 36 participants were needed to detect a medium effect size (f = 0.25). Accounting for a 5% dropout rate, a total of 38 participants were required.

the end of the experiment. £50 was given to each participant as compensation for their time. The trial was registered at www.controlled-trials.com (29th April 2014, ISRCTN70396934). Participants were recruited between 1st May 2014 and 17th August 2015, and data were collected between 20th May 2014 and 9th September 2015.

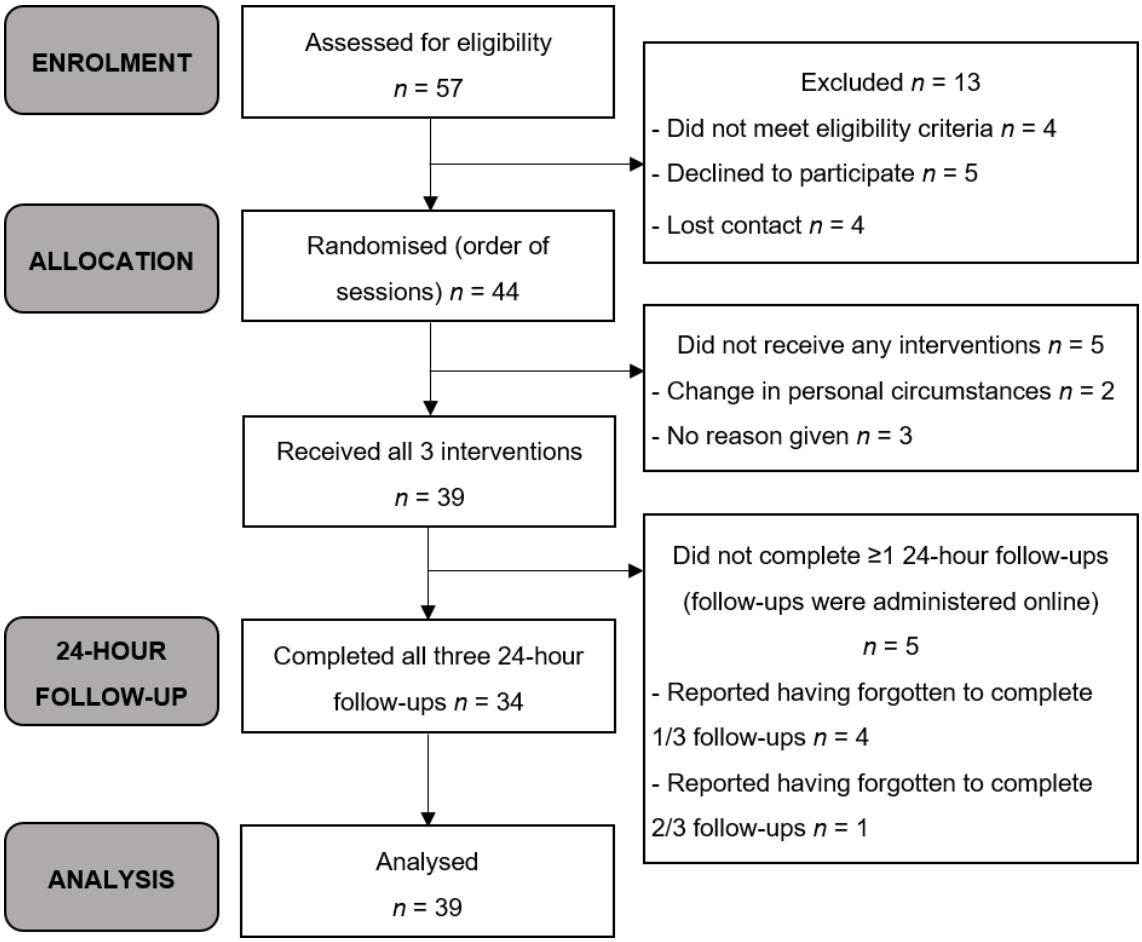


Figure 5.1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the progress through the phases of this randomised controlled trial.

5.3.2 Design and procedure

A double-blind sham-controlled crossover design was employed in which all participants received three sessions of tDCS: (i) AR/CL; (ii) AL/CR; and (iii) sham. In an effort to minimise any potential learning effects, order of stimulation was

randomised and counterbalanced across participants by a third party using the block method (block size: 6). Electrode polarity for sham sessions was determined with a random number generator (0 or 1). Due to the inclusion of two electrode montages, it was not possible for the tDCS technician to be blinded; however, the patient and the researcher administering the experimental measures remained blind throughout. An intersession interval (≥ 2 days; $M = 9.10$, $SD = 9.39$) was used to avoid any carryover effects of stimulation and, for each participant, all three sessions were held at the same time of day.

At the first appointment, participants completed several baseline assessments: demographic questionnaire, Eating Disorder Examination Questionnaire (EDE-Q; Fairburn & Beglin, 2008), and Depression Anxiety and Stress Scales (DASS-21; Lovibond & Lovibond, 1995). The following pre-tDCS measures were completed during each study session[13]: (i) TD task; (ii) Profile of Mood States (POMS; McNair et al., 1971); (iii) Positive and Negative Affect Schedule (PANAS; Watson et al., 1988); (iv) Food Challenge Task (FCT); (v) urge to binge-eat visual analogue scale (VAS); (vi) Mizes Eating Disorder Cognition Questionnaire-Revised (MEDCQ-R; Mizes et al., 2000); and (vi) blood pressure/pulse. Participants then received a 20-minute session of tDCS (AR/CL, AL/CR, or sham). Immediately post-tDCS, they repeated the pre-tDCS measures in the same order, followed by a VAS measuring the tolerability of tDCS. A follow-up questionnaire was completed 24 hours later. At the end of the third appointment, intervention acceptability and blinding success were evaluated. A schematic representation of the study procedure is provided in Figure 5.2.

[13] Previous studies have demonstrated good short-term test retest reliability for TD tasks (Weafer, Baggott, & de Wit, 2013) as well as for the POMS (McNair, Lorr, & Droppleman, 1971), PANAS (Watson, Clark, & Tellegen, 1988), and MEDCQ-R (Mizes et al., 2000).

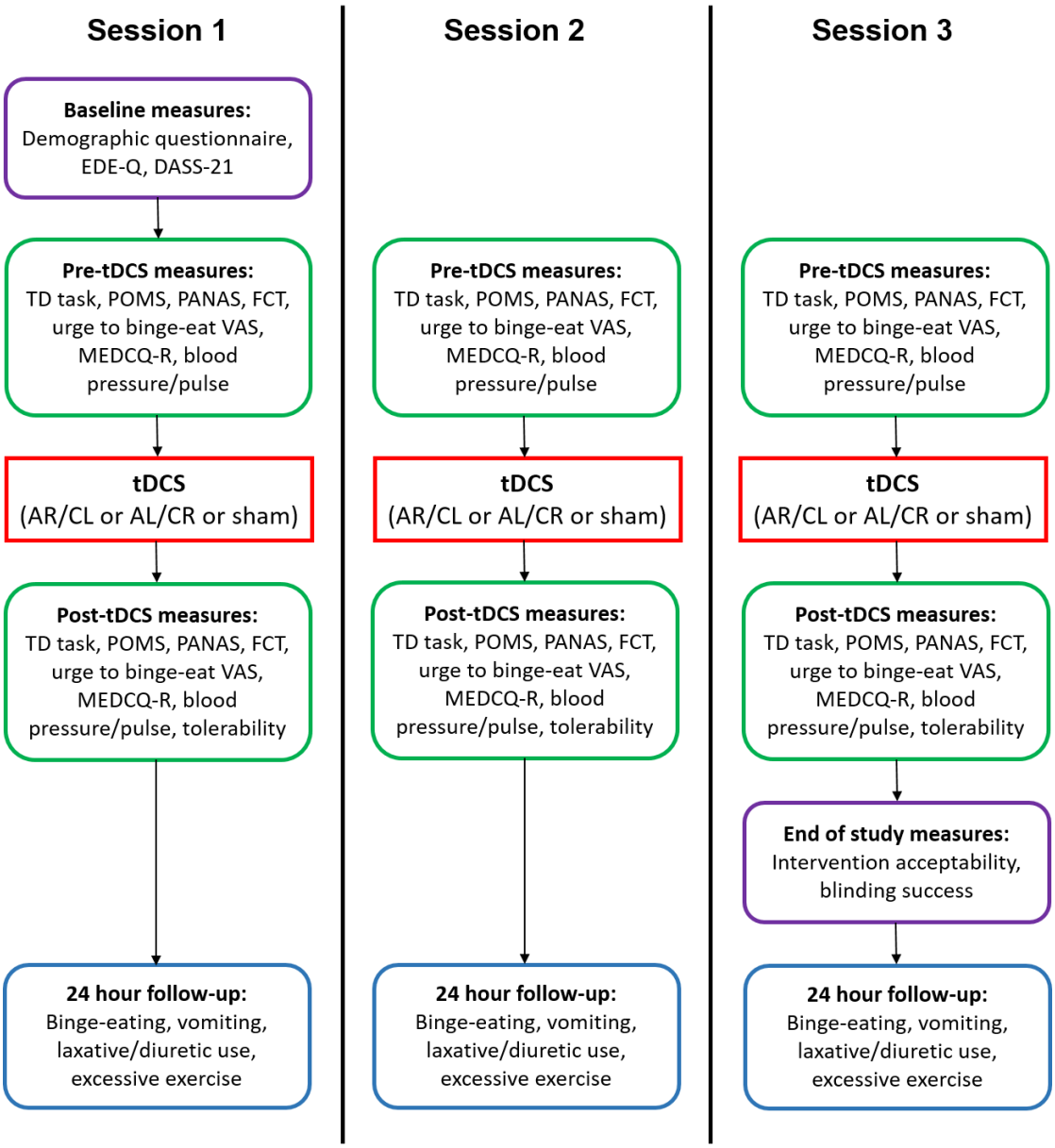


Figure 5.2 Schematic representation of study procedure.

5.3.3 Transcranial direct current stimulation

tDCS was delivered using a neuroConn® DC-STIMULATOR (20 mins, 2 mA, 10-second ramp on/off) via two 25cm^2 surface sponge electrodes soaked in 0.9% sodium chloride. In the AR/CL condition, the anode and cathode were placed over the right (F4) and left DLPFC (F3), respectively. This montage was reversed for AL/CR tDCS. The

sites of stimulation were located using the Beam F3 Location System (Beam, Borckardt, Reeves, & George, 2009), which is based on the International 10-20 system. For sham tDCS, electrode placement corresponded to one of the active conditions (see Design and procedure). To mimic real stimulation, the device's sham setting was used: a current was applied for the first 30 seconds of the session, after which it stopped automatically. Participants therefore experienced the initial tingling sensation but received no stimulation for the remaining 19.5 minutes. Our group has shown that this sham treatment cannot be distinguished from real tDCS (Kekic et al., 2014).

5.3.4 Measures

Measures are described in the order in which they were administered. The primary outcome variable was urge to binge-eat; all other outcomes were secondary.

5.3.4.1 Urge to binge-eat visual analogue scale

Participants rated their urge to binge-eat on a computerised VAS administered via Adaptive Visual Analog Scales software (Marsh-Richard, Hatzis, Mathias, Venditti, & Dougherty, 2009), which was anchored with "no urge to binge-eat" and "extreme urge to binge-eat".

5.3.4.2 Mizes Eating Disorder Cognition Questionnaire-Revised

The MEDCQ-R (formerly the Mizes Anorectic Cognitions Questionnaire-Revised; Mizes et al., 2000) is a 24-item self-report inventory which assesses cognitions in EDs. Responses are made on a Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree), yielding a global score and a score for three subscales: self-control and self-esteem, rigid weight regulation and fear of weight gain, and weight and approval.

Interpretation of the scores involves converting raw scores into T-scores using the following formula: (obtained raw score – mean)/standard deviation x 10 + 50. Appropriate normative data are published elsewhere (Peak, Mizes, & Guillard Jr, 2012). Global MEDCQ-R T-score was used as the outcome variable for this measure.

5.3.4.3 Food Challenge Task

The FCT – which involves exposure to a food video, the presentation of real food, and a series of VASs – was initially developed by our group to induce and assess food cravings, and has been administered in our laboratory in variable formats (Kekic et al., 2014; McClelland et al., 2016a; Uher et al., 2005; Van den Eynde et al., 2010; Van den Eynde, Guillaume, Broadbent, Campbell, & Schmidt, 2013). Based on recent literature (Cowdrey, Finlayson, & Park, 2013) and on feedback from participants in earlier studies (Kekic et al., 2014; McClelland et al., 2016a), several adaptations were made to the FCT for the present trial. Firstly, a new food video was created (5 mins) using clips from television advertisements. This video was piloted in 40 adults (9 males), who rated the foods shown as highly appetising (mean rating: 73.38/100) and whose hunger was significantly increased by the footage [$t(39) = -6.37$, $p < .001$, $r = 0.71$]. Secondly, the real foods presented were altered to cover four categories: high-calorie sweet (chocolate, sweets), high-calorie savoury (crisps, nuts), low-calorie sweet (orange, apple), and low-calorie savoury (table water crackers, rice cakes). Lastly, the VASs – which were computerised and administered via Adaptive Visual Analog Scales software – were modified so that both the wanting (craving) and the perceived liking of each real food were measured. For wanting, participants were asked "How much do you want some of the [food] right now?" and, for liking, they were asked "How pleasant would it be to experience the taste of the [food]?". These questions have been used previously to differentiate the wanting and liking elements of food reward (Cowdrey et al., 2013).

5.3.4.4 Temporal discounting task

TD was assessed with a hypothetical monetary choice task, modelled on an established paradigm (Steinglass et al., 2012; Weber et al., 2007). Eighty binary choices were administered in a random order: for each one participants chose between a smaller amount of money available immediately (smaller-sooner [SS] reward) and a larger amount available in 3 months (larger-later [LL] reward). Two types of decision framing were employed: Accelerate and Delay (40 binary choices in each set). In the Accelerate set, the LL reward remained at £100 and the SS reward increased from £20 to £98 in £2 increments. In the Delay set, the SS reward was fixed at £50 while the LL reward increased from £52 to £130 in £2 increments. TD was quantified by determining participants' discount factor – the magnitude of reduction in the present value of a future reward – for each choice set using a two-step procedure described elsewhere (Read, 2001; Steinglass et al., 2012; Weber et al., 2007). The value obtained ranges from 0 to 1, with smaller numbers indicating greater TD and thus a greater tendency to choose the immediate reward. The global discount factor was calculated as the mean of the Accelerate and Delay discount factors, and used as the outcome variable.

5.3.4.5 Profile of Mood States

The POMS (McNair et al., 1971) is a self-report measure containing 65 adjectives which respondents rate on a Likert scale ranging from 0 (not at all) to 4 (extremely). Participants answered in relation to how they were feeling at the time of responding ("right now"). The scale includes six factors (tension, depression, anger, vigour, fatigue, and confusion). A total mood disturbance score can also be calculated (global POMS score), which was used as the outcome variable for this questionnaire.

5.3.4.6 Positive and Negative Affect Schedule

The PANAS (Watson et al., 1988) consists of two 10-item self-report scales which measure positive and negative affect. On a Likert scale ranging from 0 (very slightly or not at all) to 4 (extremely), participants rate the extent to which they have experienced each of the 20 descriptors within a particular time frame ("right now" in the current study). Two scores are generated: positive (PANAS-positive) and negative (PANAS-negative) affect.

5.3.4.7 Tolerability, acceptability, and blinding of transcranial direct current stimulation

Tolerability was assessed with a 10cm paper-based VAS measuring level of discomfort experienced during the tDCS. Acceptability was determined by asking participants whether they would consider taking part in a therapeutic trial of tDCS (involving ~20 sessions), if it were available. The validity of the sham treatment was judged by asking participants and researchers who administered the experimental measures to identify the placebo session, and to rate their confidence in their answer on a 10cm paper-based VAS.

5.3.4.8 Follow-up questionnaire

The follow-up questionnaire was administered online (the URL was shared by email). Participants were required to state how many episodes of binge-eating, vomiting, laxative/diuretic use, and excessive exercise they had engaged in during the 24-hour period following each tDCS session.

5.3.5 Data analysis

Statistical analyses were performed on IBM® SPSS® (version 21) using a two-sided significance of 0.05. A series of boxplots indicated that there were no obvious outliers in the data. For variables with normally distributed data, effects of tDCS were evaluated using two-way 3 (stimulation: AR/CL vs. AL/CR vs. sham) x 2 (timepoint: pre-tDCS vs. post-tDCS) repeated measures ANOVAs, whereby significant stimulation x timepoint interactions indicated that the effects of stimulation varied across conditions (simple effects analyses were used to determine which conditions differed). Where data were not normally distributed, Wilcoxon signed-rank tests were used to compare pre- and post-tDCS scores for each condition separately. Friedman's one-way ANOVAs and one-way repeated measures ANOVAs were used to explore the effect of stimulation type (AR/CL vs. AL/CR vs. sham) on symptoms during the 24-hour follow-up period and on the discomfort experienced during tDCS, respectively. Blinding success was appraised using Pearson's chi-square goodness-of-fit tests. Where relevant, effect sizes (*r*) are reported. Since this was a proof-of-principle study, an exploratory analysis of multiple outcomes was used in an attempt to identify hypotheses that could be subject to more rigorous future examination. To avoid being too conservative and making Type II errors, we did not correct for multiple comparisons.

5.4 RESULTS

5.4.1 Demographic and clinical characteristics

The sample comprised 37 females and 2 males aged 18-48 (M = 25.85, SD = 6.62) with a mean BMI of 21.65 (SD = 3.20). The majority were right-handed (87.2%), described their ethnicity as "white" (74.4%), and had an annual personal income < £20,000 (61.5%). All participants were educated to A Level standard or higher (a qualification

offered to students completing secondary or pre-university education in the UK). The mean global EDE-Q score was 4.21 (*SD* = 1.06) – with 61.5% of scores above the clinically relevant cut-off (≥ 4; Rø, Reas, & Rosenvinge, 2012) – and severe or extremely severe levels of depression (≥ 21), anxiety (≥ 15), and stress (≥ 26; indexed by the DASS-21) were reported by 56.4%, 43.6%, and 35.9% of participants, respectively. Further information on clinical characteristics is provided in Table 5.1.

Table 5.1 Clinical characteristics of the study sample.

	M (*n*)	**SD (%)**	**Range**
Duration of illness (months)	110.87	95.62	4.00-528.00
Time spent in treatment (months)	22.97	42.29	0.00-183.60
Current treatment			
Psychotherapy	(13)	(33.3)	-
Pharmacotherapy	(4)	(10.3)	-
None	(22)	(56.4)	-
Been an inpatient?			
Yes	(10)	(25.6)	-
No	(29)	(74.4)	-
Bulimic behaviours per week[a]			
Binge-eating	8.08	13.80	1.00-87.50
Self-induced vomiting	8.10	14.25	0.00-88.00
Laxative/diuretic abuse	1.15	3.06	0.00-14.00
Fasting	2.44	2.44	0.00-10.00
Excessive exercise	2.16	2.57	0.00-10.00
EDE-Q[b]			
Restraint	3.92	1.21	0.60-6.00
Eating concern	3.86	1.14	1.40-6.00
Shape concern	4.68	1.24	0.75-6.00
Weight concern	4.38	1.33	1.40-6.00
Global	4.21	1.06	1.65-6.00
DASS-21[c]			
Depression	20.62	10.39	0.00-38.00
Anxiety	15.23	11.65	0.00-42.00
Stress	21.97	10.19	2.00-42.00

M, mean; SD, standard deviation; EDE-Q, Eating Disorder Examination Questionnaire; DASS-21, Depression Anxiety and Stress Scales.

[a] Self-reported during the telephone screen.

[b] Subscale and global scores can range from 0-6.

[c] Subscale scores can range from 0-42.

5.4.2 Effects of transcranial direct current stimulation

5.4.2.1 Eating disorder symptoms

Three Wilcoxon signed-rank tests demonstrated that urge to binge-eat VAS scores were reduced following active [AR/CL: Z = -2.42, p = .016, r = -0.27, AL/CR: Z = -2.52, p = .012, r = -0.28] but not sham stimulation [Z = -1.26, p = .207, r = -0.14] (Figure 5.3). For global MEDCQ-R T-score, a repeated measures ANOVA revealed a significant main effect of timepoint [F(1, 38) = 11.92, p = .001], but not stimulation [F(2, 76) = 0.30, p = .744], and a significant stimulation x timepoint interaction (with a Huynh-Feldt correction) [F(1.63, 62.02) = 3.83, p = .035] (Figure 5.4). Simple effects analyses showed that AR/CL stimulation reduced global MEDCQ-R T-scores significantly more than both AL/CR [F(1, 38) = 4.42, p = .042, r = 0.32] and sham stimulation [F(1, 38) = 5.17, p = .029, r = 0.35], and that AL/CR and sham tDCS exerted equivalent effects [F(1, 38) = 0.22, p = .643, r = 0.08]. Several Friedman's ANOVAs showed that the frequency of binge-eating, vomiting, laxative/diuretic use, and excessive exercise during the 24-hour follow-up period was comparable across the three conditions [all $p \geq .549$].

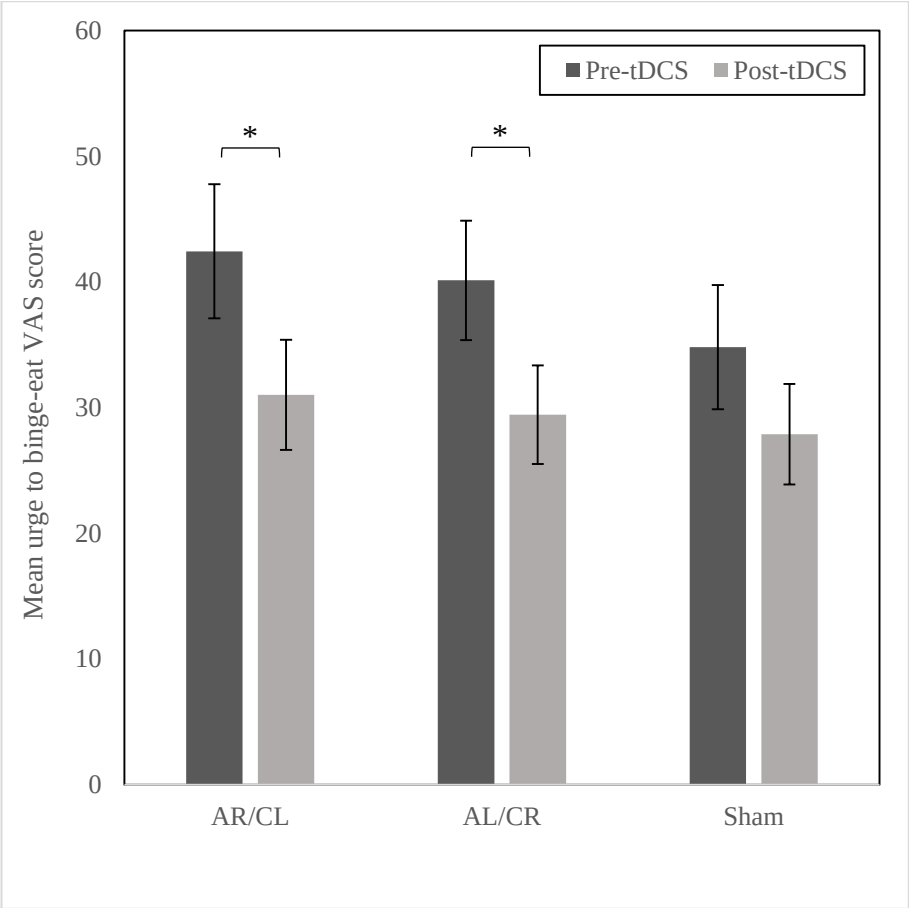


Figure 5.3 Mean urge to binge-eat visual analogue scale scores pre and post anode right/cathode left, anode left/cathode right, and sham transcranial direct current stimulation (tDCS).

VAS, visual analogue scale; AR/CL, anode right/cathode left; AL/CR, anode left/cathode right; tDCS, transcranial direct current stimulation.

* $p < .05$.

Note: pre-tDCS scores across the three conditions were not significantly different [$X^2(2) = 5.59$, $p = .061$].

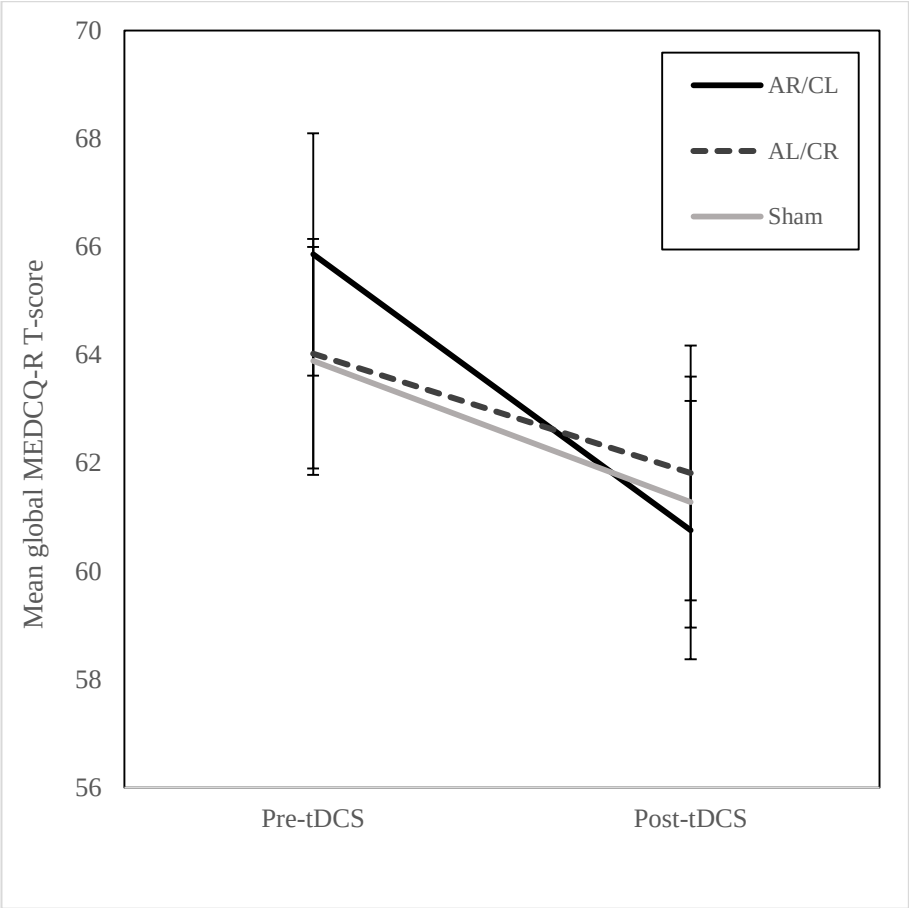


Figure 5.4 Mean global Mize's Eating Disorder Cognition Questionnaire-Revised T-scores pre and post anode right/cathode left, anode left/cathode right, and sham transcranial direct current stimulation (tDCS).

MEDCQ-R, Mize's Eating Disorder Cognition Questionnaire-Revised; AR/CL, anode right/cathode left; AL/CR, anode left/cathode right; tDCS, transcranial direct current stimulation.

Note: pre-tDCS scores across the three conditions were not significantly different [$F(2, 76) = 2.05$, $p = .136$].

5.4.2.2 Wanting and liking of food

Repeated measures ANOVAs were conducted to assess the effects of tDCS on the wanting and liking of each food separately, all foods together, sweet foods, savoury foods, high-calorie foods, low-calorie foods, sweet high-calorie foods, sweet low-calorie foods, savoury high-calorie foods, and savoury low-calorie foods. There was a significant main effect of timepoint across all liking [all $p \leq .020$] but no wanting

variables [all $p \geq .091$]. Non-significant main effects of stimulation [all $p \geq .123$] and stimulation x timepoint interactions were observed for all wanting/liking outcomes [all $p \geq .100$].

5.4.2.3 Temporal discounting behaviour

Wilcoxon signed-rank tests showed that post-tDCS global discount factors were significantly higher (indicating increased self-regulatory control) than pre-tDCS scores following AR/CL [Z = -2.91, p = .004, r = -0.33] and AL/CR [Z = -3.04, p = .002, r = -0.34] tDCS, but not sham tDCS [Z = -1.74, p = .083, r = -0.20] (Figure 5.5).

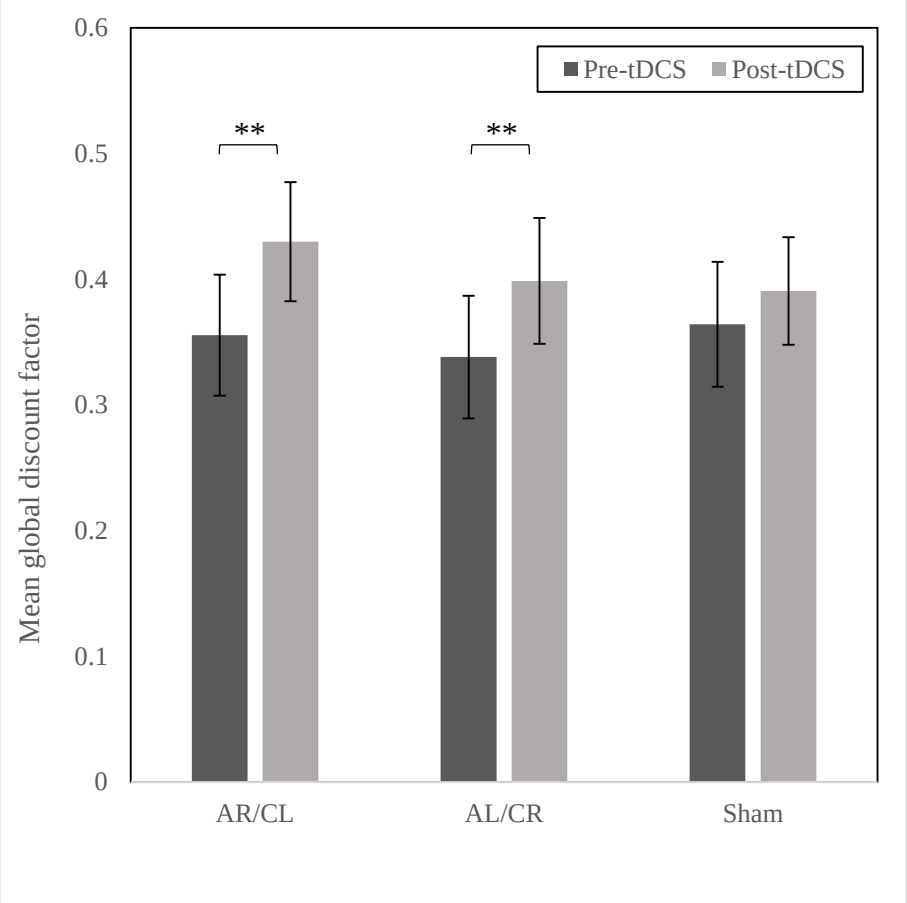


Figure 5.5 Mean global discount factors pre and post anode right/cathode left, anode left/cathode right, and sham transcranial direct current stimulation (tDCS).

AR/CL, anode right/cathode left; AL/CR, anode left/cathode right; tDCS, transcranial direct current stimulation.

** $p < .01$.

Note: pre-tDCS scores across the three conditions were not significantly different [$X^2(2) = 1.61$, $p = .446$].

5.4.2.4 Mood

A repeated measures ANOVA showed a significant main effect of timepoint [$F(1, 35) = 21.73$, $p = < .001$], no main effect of stimulation [$F(1.47, 51.44) = 2.19$, $p = .135$], and a trend towards a significant stimulation x timepoint interaction for global POMS score [$F(2, 70) = 2.92$, $p = .060$]. Simple effects analyses demonstrated that AR/CL tDCS lowered global POMS scores significantly more than sham stimulation [$F(1, 35) = 5.15$, $p = .030$, $r = 0.36$]. In addition, although the two active conditions exerted similar effects on global POMS scores [$F(1, 35) = 0.82$, $p = .371$, $r = 0.15$], AL/CR tDCS was not significantly superior to sham stimulation [$F(1, 35) = 2.32$, $p = .137$, $r = 0.25$]. Two further repeated measures ANOVAs revealed a significant main effect of timepoint for PANAS-negative [$F(1, 38) = 16.72$, $p < .001$] but not PANAS-positive [$F(1, 38) = 0.62$, $p = .435$] score, and non-significant main effects of stimulation [all $p \geq .395$] and interaction terms [all $p \geq .516$] for both variables.

5.4.3 Success of the blinding procedure

Neither participants [41.0% correct; $\chi^2(1) = 1.04$, $p = .308$] nor researchers who administered the experimental measures [40.5% correct; $\chi^2(1) = 0.87$, $p = .352$] distinguished real from sham tDCS at a rate better than chance. Both parties expressed little confidence in their identification of the placebo session (10cm VAS, participants: $M = 3.18$, $SD = 2.37$, researchers: $M = 0.58$, $SD = 1.44$).

5.4.4 Safety, tolerability and acceptability of transcranial direct current stimulation

Three repeated measures ANOVAs revealed no effect of stimulation type on blood pressure or pulse [all $p \geq .104$]. An additional repeated measures ANOVA revealed a main effect of stimulation on discomfort ratings [$F(2, 76) = 5.82$, $p = .004$]. Simple effects analyses showed that both real conditions were rated as more uncomfortable than sham tDCS [AR/CL: $F(1, 38) = 7.14$, $p = .011$, $r = 0.40$, AL/CR: $F(1, 38) = 10.05$, $p = .003$, $r = 0.46$]. Nevertheless, all sessions were associated with low levels of discomfort (10cm VAS, AR/CL: $M = 2.82$, $SD = 2.40$, AL/CR: $M = 2.88$, $SD = 2.23$, sham: $M = 1.72$, $SD = 1.54$). Thirty-eight of 39 participants indicated that they would consider taking part in a therapeutic trial of tDCS (the remaining participant was unsure).

5.5 DISCUSSION

This is the first study to investigate the effects of tDCS in BN. The results provide positive proof-of-principle for the clinical utility of bilateral tDCS applied to the DLPFC in this patient population. Specifically, AR/CL tDCS transiently reduced the severity of ED-related cognitions (indexed by the MEDCQ-R) when compared with AL/CR and sham tDCS. In addition, both AR/CL and AL/CR suppressed the urge to binge-eat and increased the level of self-regulatory control exercised during a TD task. Compared to sham stimulation, mood (assessed with the POMS) improved after AR/CL but not AL/CR tDCS. Lastly, the three tDCS sessions exerted equivalent effects on the wanting and liking of food and on bulimic behaviours during the 24-hour follow-up period.

The decrease in symptoms of BN is consistent with emerging evidence demonstrating that modulation of the DLPFC with NIBS can induce therapeutic effects in EDs (Burgess et al., 2016; Khedr et al., 2014; McClelland et al., 2013; McClelland et al., 2016a; McClelland, Kekic, Campbell, & Schmidt, 2016b). Though only modest improvements were recorded and no effects on actual bulimic behaviours were observed, cortical excitability changes generated by a single session of tDCS are slight (~20%) and appear to diminish approximately 1-2 hours post-stimulation (Alonzo, Brassil, Taylor, Martin, & Loo, 2012; Monte-Silva et al., 2013). Conversely, tDCS interventions comprising multiple sessions have been shown to produce consolidative and cumulative excitatory effects (Alonzo et al., 2012), and to elicit long-lasting clinical gains in several psychiatric disorders (Kekic et al., 2016b), including anorexia nervosa (Khedr et al., 2014). The results of this study therefore provide a strong rationale for conducting a tDCS treatment trial in BN.

Our finding that active but not sham tDCS reduced TD behaviour contributes to research showing that this presumed stable personality trait can be altered acutely by experimental manipulation (Gray & MacKillop, 2015; Koffarnus, Jarmolowicz, Mueller, & Bickel, 2013; McClelland et al., 2016a), and suggests that the absence of change previously documented by our group (Kekic et al., 2014) might be attributable to differences in the TD task/measurement of discounting. It also supports a key role for the DLPFC in self-regulatory control, and provides some insight into the neurocognitive mechanisms through which tDCS might exert its therapeutic effects. Further mechanistic inferences can be drawn from our finding that real versus sham tDCS reduced total mood disturbance (though only at trend level), which corresponds to data from the depression literature (Meron, Hedger, Garner, & Baldwin, 2015). As negative

affect is generally elevated prior to binge-eating and purging (Berg et al., 2013), improvements in mood are likely to facilitate improvements in clinical symptoms.

In this study, real versus sham stimulation had no impact on the wanting or liking of a selection of sweet and savoury high- and low-calorie foods, which contradicts the anti-craving effects of tDCS reported previously (Fregni et al., 2008; Goldman et al., 2011; Kekic et al., 2014). Nevertheless, these prior studies were conducted in healthy individuals, whose cravings may have been less intense and more modifiable. It may also be that our method of assessment lacked sensitivity, since the craving index in our earlier study (Kekic et al., 2014) incorporated ratings of the sensory properties of the foods presented (i.e., smell, taste, and appearance), and cravings are known to represent desire for particular sensory stimulation (Weingarten & Elston, 1990). Alternatively, motivational tendencies towards food might be best captured with tasks assessing implicit as opposed to explicit wanting, such as those measuring reaction time (Cowdrey et al., 2013) or saccadic eye movement (Fregni et al., 2008). Another explanation for the lack of effect of tDCS on food wanting and liking relates to the neural bases of these constructs. Food reward processing is supported by ventral limbic frontostriatal circuits and, whilst DLPFC modulation has the potential to impact these pathways via their overlap with dorsal cognitive networks (Haber, 2016), they were not directly targeted by tDCS in this trial.

The polarity effect identified in the present study – which favoured AR/CL over AL/CR tDCS – is in agreement with data from individuals with frequent food cravings (Fregni et al., 2008), and suggests that ED cognitions and mood disturbance may be hemispherically lateralised in BN. Indeed, cortical asymmetry has been reported in relation to a number of ED symptoms; for example, overeating and decision-making

impairments have been associated with reduced function in the right prefrontal cortex (Alonso-Alonso & Pascual-Leone, 2007), while disinhibition and appetitive responsivity have been linked to greater left-sided prefrontal activation (Ochner, Green, van Steenburgh, Kounios, & Lowe, 2009). These findings support the therapeutic potential of anodal (excitatory) and cathodal (inhibitory) modulation of the right and left DLPFC, respectively, but do not explain why AL/CR tDCS (and excitatory rTMS to the left DLPFC; Van den Eynde et al., 2010) too produces beneficial effects. It is also unclear why AL/CR stimulation failed to improve mood in this study, when this tDCS montage has been successfully used to treat major depression (Meron et al., 2015). Additional neuroimaging data may foster a greater understanding of brain laterality in BN.

This study has several limitations. Firstly, by chance, there was a trend for pre-tDCS urge to binge-eat scores to differ across the conditions: slightly lower values were obtained before sham tDCS than before AR/CL and AL/CR tDCS (Figure 5.3), allowing less scope for improvement in the sham session. Similarly, pre-tDCS MEDCQ-R scores appeared to be highest before AR/CL tDCS (Figure 5.4), although this difference did not approach significance. Secondly, due to the high levels of psychiatric comorbidity associated with BN (O'Brien & Vincent, 2003), we did not exclude individuals with co-occurring mental disorders. While it seems unlikely, it is not possible to state whether an effect of tDCS on comorbid psychiatric symptoms contributed to the findings (Sauvaget et al., 2015). Thirdly, we included both left- and right-handed participants, and handedness influences the effects of rTMS in BN (Van den Eynde et al., 2012). Fourthly, although the researcher administering the experimental measures was blind to the stimulation condition, we cannot rule out the possibility that participants were influenced by interaction with the unblinded tDCS

technician. Lastly, data on ED symptoms immediately after stimulation were gathered using self-report psychological measures. This limits the clinical applicability of our findings since the principal goal of BN treatments is normalisation of eating behaviour.

5.6 CONCLUSIONS

The current research provides preliminary evidence that bilateral tDCS to the DLPFC has the potential to induce therapeutic effects in BN, at least temporarily. It also elucidates possible mechanisms of action and informs the design of future trials, particularly in relation to electrode montage selection. While only modest conclusions can be drawn regarding the clinical utility of tDCS in BN, our findings offer support and justification for studies involving multi-session protocols.

5.7 REFERENCES

Alonso-Alonso, M., & Pascual-Leone, A. (2007). The right brain hypothesis for obesity. *JAMA, 297*(16), 1819-1822.

Alonzo, A., Brassil, J., Taylor, J. L., Martin, D., & Loo, C. K. (2012). Daily transcranial direct current stimulation (tDCS) leads to greater increases in cortical excitability than second daily transcranial direct current stimulation. *Brain Stimulation, 5*(3), 208-213.

Arcelus, J., Mitchell, A. J., Wales, J., & Nielsen, S. (2011). Mortality rates in patients with anorexia nervosa and other eating disorders: A meta-analysis of 36 studies. *Archives of General Psychiatry, 68*(7), 724-731.

Bartholdy, S., Dalton, B., O'Daly, O. G., Campbell, I. C., & Schmidt, U. (2016). A systematic review of the relationship between eating, weight and inhibitory control using the stop signal task. *Neuroscience and Biobehavioral Reviews, 64*, 35-62.

Beam, W., Borckardt, J. J., Reeves, S. T., & George, M. S. (2009). An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. *Brain Stimulation, 2*(1), 50-54.

Berg, K. C., Crosby, R. D., Cao, L., Peterson, C. B., Engel, S. G., Mitchell, J. E., & Wonderlich, S. A. (2013). Facets of negative affect prior to and following binge-only, purge-only, and binge/purge events in women with bulimia nervosa. *Journal of Abnormal Psychology, 122*(1), 111-118.

Berner, L. A., & Marsh, R. (2014). Frontostriatal circuits and the development of bulimia nervosa. *Frontiers in Behavioral Neuroscience, 8*, 395.

Bohon, C., & Stice, E. (2012). Negative affect and neural response to palatable food intake in bulimia nervosa. *Appetite, 58*(3), 964-970.

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., . . . Fregni, F. (2012). Clinical research with transcranial direct current stimulation (tDCS): Challenges and future directions. *Brain Stimulation, 5*(3), 175-195.

Burgess, E. E., Sylvester, M. D., Morse, K. E., Amthor, F. R., Mrug, S., Lokken, K. L., . . . Boggiano, M. M. (2016). Effects of transcranial direct current stimulation (tDCS) on binge-eating disorder. *International Journal of Eating Disorders*.

Cowdrey, F. A., Finlayson, G., & Park, R. J. (2013). Liking compared with wanting for high- and low-calorie foods in anorexia nervosa: Aberrant food reward even after weight restoration. *American Journal of Clinical Nutrition, 97*(3), 463-470.

Diana, M. (2011). The dopamine hypothesis of drug addiction and its potential therapeutic value. *Frontiers in Psychiatry, 2*, 64.

Fairburn, C. G., & Beglin, S. (2008). Eating Disorder Examination. In C. G. Fairburn (Ed.), *Cognitive Behavior Therapy and Eating Disorders* (pp. 265-308). New York: Guilford Press.

Farmer, R. F., Nash, H. M., & Field, C. E. (2001). Disordered eating behaviors and reward sensitivity. *Journal of Behavior Therapy and Experimental Psychiatry, 32*(4), 211-219.

Fregni, F., Orsati, F., Pedrosa, W., Fecteau, S., Tome, F. A. M., Nitsche, M. A., . . . Boggio, P. S. (2008). Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. *Appetite, 51*(1), 34-41.

Friederich, H.-C., Wu, M., Simon, J. J., & Herzog, W. (2013). Neurocircuit function in eating disorders. *International Journal of Eating Disorders, 46*(5), 425-432.

Garcia-Garcia, I., Narberhaus, A., Marques-Iturria, I., Garolera, M., Radoi, A., Segura, B., . . . Jurado, M. A. (2013). Neural responses to visual food cues: Insights from functional magnetic resonance imaging. *European Eating Disorders Review, 21*(2), 89-98.

Gluck, M. E., Alonso-Alonso, M., Piaggi, P., Weise, C. M., Jumpertz-von Schwartzenberg, R., Reinhardt, M., . . . Krakoff, J. (2015). Neuromodulation targeted to the prefrontal cortex induces changes in energy intake and weight loss in obesity. *Obesity, 23*(11), 2149-2156.

Goldman, R. L., Borckardt, J. J., Frohman, H. A., O'Neil, P. M., Madan, A., Campbell, L. K., . . . George, M. S. (2011). Prefrontal cortex transcranial direct current stimulation (tDCS) temporarily reduces food cravings and increases the self-reported ability to resist food in adults with frequent food craving. *Appetite, 56*(3), 741-746.

Gray, J. C., & MacKillop, J. (2015). Impulsive delayed reward discounting as a genetically-influenced target for drug abuse prevention: A critical evaluation. *Frontiers in Psychology, 6*, 1104.

Haber, S. N. (2016). Corticostriatal circuitry. *Dialogues in Clinical Neuroscience, 18*(1), 7-21.

Hare, T. A., Camerer, C. F., & Rangel, A. (2009). Self-control in decision-making involves modulation of the vmPFC valuation system. *Science, 324*(5927), 646-648.

Hausmann, A., Mangweth, B., Walpoth, M., Hoertnagel, C., Kramer-Reinstadler, K., Rupp, C. I., & Hinterhuber, H. (2004). Repetitive transcranial magnetic stimulation (rTMS) in the double-blind treatment of a depressed patient suffering from bulimia nervosa: A case report. *International Journal of Neuropsychopharmacology, 7*(3), 371-373.

Heatherton, T. F., & Wagner, D. D. (2011). Cognitive neuroscience of self-regulation failure. *Trends in cognitive sciences, 15*(3), 132-139.

Hudson, J. I., Hiripi, E., Pope Jr, H. G., & Kessler, R. C. (2007). The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biological Psychiatry, 61*(3), 348-358.

Kekic, M., Bartholdy, S., Cheng, J., McClelland, J., Boysen, E., Musiat, P., . . . Schmidt, U. (2016a). Increased temporal discounting in bulimia nervosa. *International Journal of Eating Disorders*, *49*(12), 1077-1081.

Kekic, M., Boysen, E., Campbell, I. C., & Schmidt, U. (2016b). A systematic review of the clinical efficacy of transcranial direct current stimulation (tDCS) in psychiatric disorders. *Journal of Psychiatric Research, 74*, 70-86.

Kekic, M., McClelland, J., Campbell, I., Nestler, S., Rubia, K., David, A. S., & Schmidt, U. (2014). The effects of prefrontal cortex transcranial direct current stimulation (tDCS) on food craving and temporal discounting in women with frequent food cravings. *Appetite, 78*, 55-62.

Khedr, E. M., Elfetoh, N. A., Ali, A. M., & Noamany, M. (2014). Anodal transcranial direct current stimulation over the dorsolateral prefrontal cortex improves anorexia nervosa: A pilot study. *Restorative Neurology and Neuroscience*, *32*(6), 789-797.

Koffarnus, M. N., Jarmolowicz, D. P., Mueller, E. T., & Bickel, W. K. (2013). Changing delay discounting in the light of the competing neurobehavioral decision systems theory: A review. *Journal of the Experimental Analysis of Behavior, 99*(1), 32-57.

Lovibond, S. H., & Lovibond, P. F. (1995). *Manual for the Depression Anxiety Stress Scales* (2nd ed.). Sydney: Psychology Foundation.

Loxton, N. J., & Dawe, S. (2001). Alcohol abuse and dysfunctional eating in adolescent girls: The influence of individual differences in sensitivity to reward and punishment. *International Journal of Eating Disorders, 29*(4), 455-462.

Marsh-Richard, D. M., Hatzis, E. S., Mathias, C. W., Venditti, N., & Dougherty, D. M. (2009). Adaptive Visual Analog Scales (AVAS): A modifiable software program for the creation, administration, and scoring of visual analog scales. *Behavior Research Methods, 41*(1), 99-106.

Marsh, R., Horga, G., Wang, Z., Wang, P., Klahr, K. W., Berner, L. A., . . . Peterson, B. S. (2011). An FMRI study of self-regulatory control and conflict resolution in adolescents with bulimia nervosa. *The American Journal of Psychiatry, 168*(11), 1210-1220.

Marsh, R., Steinglass, J. E., Gerber, A. J., Graziano O'Leary, K., Wang, Z., Murphy, D., . . . Peterson, B. S. (2009). Deficient activity in the neural systems that mediate self-regulatory control in bulimia nervosa. *Archives of General Psychiatry, 66*(1), 51-63.

Mauler, B. I., Hamm, A. O., Weike, A. I., & Tuschen-Caffier, B. (2006). Affect regulation and food intake in bulimia nervosa: Emotional responding to food cues after deprivation and subsequent eating. *Journal of Abnormal Psychology, 115*(3), 567-579.

McClelland, J., Bozhilova, N., Campbell, I., & 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.

McClelland, J., Kekic, M., Bozhilova, N., Nestler, S., Van Den Eynde, F., David, A., . . . Schmidt, U. (2016a). A randomised controlled trial of neuronavigated repetitive transcranial magnetic stimulation in anorexia nervosa. *PLOS ONE, 11*(3).

McClelland, J., Kekic, M., Campbell, I. C., & Schmidt, U. (2016b). Repetitive transcranial magnetic stimulation (rTMS) treatment in enduring anorexia nervosa: A case series. *European Eating Disorders Review, 24*(2), 157-163.

McNair, D. M., Lorr, M., & Droppleman, L. F. (1971). *Manual for the Profile of Mood States*. San Diego, CA: Educational and Industrial Testing Services.

Meron, D., Hedger, N., Garner, M., & Baldwin, D. S. (2015). Transcranial direct current stimulation (tDCS) in the treatment of depression: Systematic review and meta-analysis of efficacy and tolerability. *Neuroscience and Biobehavioral Reviews, 57*, 46-62.

Mizes, J. S., Christiano, B., Madison, J., Post, G., Seime, R., & Varnado, P. (2000). Development of the Mizes Anorectic Cognitions Questionnaire-Revised: Psychometric properties and factor structure in a large sample of eating disorder patients. *International Journal of Eating Disorders, 28*(4), 415-421.

Monte-Silva, K., Kuo, M.-F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., & Nitsche, M. A. (2013). Induction of Late LTP-Like Plasticity in the Human Motor Cortex by Repeated Non-Invasive Brain Stimulation. *Brain Stimulation, 6*(3), 424-432.

National Institute for Health and Care Excellence. (2004). Eating disorders: Core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders. . http://www.nice.org.uk/guidance/cg9/evidence/full-guideline-243824221

O'Brien, K. M., & Vincent, N. K. (2003). Psychiatric comorbidity in anorexia and bulimia nervosa: Nature, prevalence, and causal relationships. *Clinical Psychology Review, 23*(1), 57-74.

Ochner, C. N., Green, D., van Steenburgh, J. J., Kounios, J., & Lowe, M. R. (2009). Asymmetric prefrontal cortex activation in relation to markers of overeating in obese humans. *Appetite, 53*(1), 44-49.

Peak, N. J., Mizes, J. S., & Guillard Jr, R. P. (2012). Investigating the use of the Mizes Anorectic Cognitions Questionnaire in a community sample of racially diverse high school males and females. *Eating Behaviors, 13*(2), 94-99.

Penas-Lledo, E., Aguera, Z., Sanchez, I., Gunnard, K., Jimenez-Murcia, S., & Fernandez-Aranda, F. (2013). Differences in cognitive behavioral therapy dropout rates between bulimia nervosa subtypes based on drive for thinness and depression. *Psychotherapy and Psychosomatics, 82*(2), 125-126.

Poulsen, S., Lunn, S., Daniel, S. I. F., Folke, S., Mathiesen, B. B., Katznelson, H., & Fairburn, C. G. (2014). A randomized controlled trial of psychoanalytic psychotherapy or cognitive-behavioral therapy for bulimia nervosa. *The American Journal of Psychiatry, 171*(1), 109-116.

Read, D. (2001). Is time-discounting hyperbolic or subadditive? *Journal of Risk and Uncertainty, 23*(1), 5-32.

Rø, Ø., Reas, D. L., & Rosenvinge, J. (2012). The impact of age and BMI on Eating Disorder Examination Questionnaire (EDE-Q) scores in a community sample. *Eating Behaviors, 13*(2), 158-161.

Sauvaget, A., Trojak, B., Bulteau, S., Jiménez-Murcia, S., Fernández-Aranda, F., Wolz, I., . . . Grall-Bronnec, M. (2015). Transcranial direct current stimulation (tDCS) in behavioral and food addiction: A systematic review of efficacy, technical, and methodological issues. *Frontiers in Neuroscience, 9*, 349.

Smink, F. R., van Hoeken, D., & Hoek, H. W. (2012). Epidemiology of eating disorders: Incidence, prevalence and mortality rates. *Current Psychiatry Reports, 14*(4), 406-414.

Steinglass, J. E., Figner, B., Berkowitz, S., Simpson, H. B., Weber, E. U., & Walsh, B. T. (2012). Increased capacity to delay reward in anorexia nervosa. *Journal of the International Neuropsychological Society, 18*(4), 773-780.

Stice, E., Marti, C. N., & Rohde, P. (2013). Prevalence, incidence, impairment, and course of the proposed DSM-5 eating disorder diagnoses in an 8-year prospective community study of young women. *Journal of Abnormal Psychology, 122*(2), 445-457.

Stice, E., Telch, C. F., & Rizvi, S. L. (2000). Development and validation of the Eating Disorder Diagnostic Scale: A brief self-report measure of anorexia, bulimia, and binge-eating disorder. *Psychological Assessment, 12*(2), 123-131.

Uher, R., Yoganathan, D., Mogg, A., Eranti, S. V., Treasure, J., Campbell, I. C., . . . Schmidt, U. (2005). Effect of left prefrontal repetitive transcranial magnetic stimulation on food craving. *Biological Psychiatry, 58*(10), 840-842.

Van den Eynde, F., Broadbent, H., Guillaume, S., Claudino, A., Campbell, I. C., & Schmidt, U. (2012). Handedness, repetitive transcranial magnetic stimulation and bulimic disorders. *European Psychiatry, 27*(4), 290-293.

Van den Eynde, F., Claudino, A. M., Mogg, A., Horrell, L., Stahl, D., Ribeiro, W., . . . Schmidt, U. (2010). Repetitive transcranial magnetic stimulation reduces cue-induced food craving in bulimic disorders. *Biological Psychiatry, 67*(8), 793-795.

Van den Eynde, F., Guillaume, S., Broadbent, H., Campbell, I. C., & Schmidt, U. (2013). Repetitive transcranial magnetic stimulation in anorexia nervosa: A pilot study. *European Psychiatry, 28*(2), 98-101.

Wagner, D. D., Boswell, R. G., Kelley, W. M., & Heatherton, T. F. (2012). Inducing negative affect increases the reward value of appetizing foods in dieters. *Journal of Cognitive Neuroscience, 24*(7), 1625-1633.

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology, 54*(6), 1063-1070.

Weafer, J., Baggott, M. J., & de Wit, H. (2013). Test-retest reliability of behavioral measures of impulsive choice, impulsive action, and inattention. *Experimental and Clinical Psychopharmacology, 21*(6), 475-481.

Weber, E. U., Johnson, E. J., Milch, K. F., Chang, H., Brodscholl, J. C., & Goldstein, D. G. (2007). Asymmetric discounting in intertemporal choice: A query-theory account. *Psychological Science, 18*(6), 516-523.

Weingarten, H. P., & Elston, D. (1990). The phenomenology of food cravings. *Appetite, 15*(3), 231-246.

Wierenga, C. E., Ely, A., Bischoff-Grethe, A., Bailer, U. F., Simmons, A. N., & Kaye, W. H. (2014). Are extremes of consumption in eating disorders related to an altered balance between reward and inhibition? *Frontiers in Behavioral Neuroscience, 8,* 410.

Wu, M., Brockmeyer, T., Hartmann, M., Skunde, M., Herzog, W., & Friederich, H.-C. (2016). Reward-related decision making in eating and weight disorders: A systematic review and meta-analysis of the evidence from neuropsychological studies. *Neuroscience and Biobehavioral Reviews, 61,* 177-196.

Chapter 6. General discussion

6.1 HYPOTHESES TESTED

The overarching aim of this research was to investigate the therapeutic utility of transcranial direct current stimulation (tDCS) in bulimia nervosa (BN). Four major hypotheses were tested:

(1) Exiting literature demonstrates that tDCS induces beneficial clinical effects in several psychiatric disorders, and may therefore have therapeutic potential in BN (chapter 2).

(2) A single session of real versus sham tDCS applied to the bilateral dorsolateral prefrontal cortex (DLPFC) will temporarily reduce food craving and temporal discounting (a marker of low self-regulatory control denoting a preference towards more immediate rewards) in healthy women with frequent food cravings – again, suggesting tDCS may have therapeutic potential in BN (chapter 3).

(3) Individuals with BN will display increased temporal discounting (i.e., poor self-regulatory control) relative to healthy comparison participants (chapter 4).

(4) A single session of real versus sham tDCS applied to the bilateral DLPFC will temporarily reduce symptoms, improve mood, alter food wanting/liking, and decrease temporal discounting (i.e., improve self-regulatory control) in individuals with BN (chapter 5).

6.2 SUMMARY OF THE FINDINGS

The first hypothesis was tested in a systematic review of the clinical efficacy of tDCS across all psychiatric disorders (chapter 2). Sixty-six studies were appraised in total and, overall, data suggested that tDCS interventions comprising multiple sessions can

ameliorate symptoms of major depression, schizophrenia, and substance use disorders, both acutely and in the long-term. Limited support for the therapeutic potential of tDCS in obsessive compulsive disorder, generalised anxiety disorder, and anorexia nervosa (AN) was also obtained. Although a considerable proportion of the evidence was derived from case studies/series, and several methodological and ethical issues were identified, this review supports hypothesis one and provides a rationale for research investigating the clinical utility of tDCS in individuals with BN.

A randomised controlled trial (RCT) in 17 healthy women with frequent food cravings was conducted to test hypothesis two (chapter 3). Results showed that a single session of real versus sham tDCS applied to the bilateral DLPFC (anode right/cathode left) transiently reduced cue-induced craving for sweet but not savoury food, and had no effect on temporal discounting or actual food consumption during a free-eating task. In addition, participants who exhibited lower rates of temporal discounting (i.e., greater self-regulatory control) were more susceptible to the anti-craving effects of stimulation than those who displayed higher rates of temporal discounting (i.e., poorer self-regulatory control). Lastly, the blinding procedure employed was effective and tDCS was shown to be a safe and tolerable intervention. Since tDCS temporarily altered anticipatory food reward processing but had no effect on self-regulatory control, these findings provide partial support for hypothesis two and for the application of tDCS in BN.

The third hypothesis was tested in a cross-sectional study examining temporal discounting behaviour in 39 patients with BN as compared with 53 healthy controls (chapter 4). Consistent with expectations, the BN group showed greater temporal discounting (i.e., poorer self-regulatory control) during a computerised task – even after

controlling for several confounding variables – as well as a decreased self-reported capacity to delay gratification (the reverse of temporal discounting). Temporal discounting was not significantly correlated with body mass index or with any clinical outcomes (i.e., general/eating disorder [ED] psychopathology and illness duration/severity) among individuals with BN, whilst delaying gratification was negatively related to anxiety and stress only. Given the between-group differences observed, findings from this study substantiate the idea that altered self-regulatory control could be a relevant target for intervention among individuals with BN, and thus offer support for the testing of hypothesis four.

To test the fourth major hypothesis, an RCT of single-session tDCS applied to the bilateral DLPFC was carried out in 39 patients with BN[14] (chapter 5). The design of this study was informed by the preliminary RCT discussed above: several changes were made to the food-exposure task (see section 5.3.4.3), a new temporal discounting task was created that was considered more sensitive, and a third tDCS condition was added to the protocol (anode left/cathode right). Results revealed that, firstly, anode right/cathode left tDCS reduced ED cognitions when compared to anode left/cathode right and sham tDCS. Secondly, both active conditions suppressed the self-reported urge to binge-eat and increased self-regulatory control during the temporal discounting task. Thirdly, compared to sham stimulation, mood improved after anode right/cathode left but not anode left/cathode right tDCS. Fourthly, the three tDCS sessions had comparable effects on the wanting/liking of food and on bulimic behaviours during the 24 hours post-stimulation. Lastly, the intervention demonstrated safety and high tolerability/acceptability among participants. Since tDCS transiently improved

[14] These patients were the same ones who took part in the study presented in chapter 4.

symptoms, mood, and self-regulatory control but had no impact upon food wanting/liking, the findings from this experiment partially support hypothesis four.

6.3 IMPLICATIONS

6.3.1 Treatment of bulimia nervosa

The results of studies presented in this thesis suggest that tDCS may have potential for development as a treatment for adult BN. This is an exciting prospect given the sizeable proportion of patients (~23%; Steinhausen & Weber, 2009) who do not respond to available psychological and pharmacological therapies for the disorder. Nevertheless, despite considerable data supporting the clinical utility of tDCS in major depression and schizophrenia (see chapter 2), neither the US Food and Drug Administration Agency nor the UK National Institute for Health and Care Excellence have approved the use of this neuromodulation tool for these conditions. Therefore, even if evidence of efficacy in BN accumulates, it will probably be many years before tDCS is used to treat individuals with this ED.

6.3.2 Neurobiology of bulimia nervosa

The ability of tDCS to transiently ameliorate symptoms of BN – reported in chapter 5 of this thesis – provides evidence that the condition has a neural basis. Furthermore, the concurrent reduction in temporal discounting offers indirect support for the self-regulation neurocircuit model of BN (see section 1.2.5.1), and for the involvement of the DLPFC and wider dorsal cognitive circuitry in the pathogenesis of the disorder. Improvements in symptoms were not accompanied by alterations in the wanting or liking of food, hence the food reward processing neurocircuit model of BN (see section 1.2.5.2) was not substantiated. Nevertheless, the ventral frontostriatal circuits implicated

in this model were not directly targeted by tDCS. Alternatively, the observation that food craving was reduced by DLPFC tDCS among healthy 'food cravers' raises the possibility that the null result in BN was related to differences in the task administered (see section 5.5).

Figure 6.1 shows the neurobiological model of BN, initially presented in section 1.2.8, amended to incorporate findings from the current research. According to this model, dysregulated overlapping dorsal cognitive and ventral limbic frontostriatal neurocircuits contribute to impaired self-regulatory control and food reward processing, respectively. The combination of these behavioural maladies leads to binge-eating, which is made more likely by negative affect. Compensatory behaviours, intended to prevent weight gain, ensue due to an over-concern with body weight and shape. This cycle is repeated and maintained as a result of altered habit learning processes caused by disturbances in frontostriatal circuitry, ultimately contributing to the development of BN.

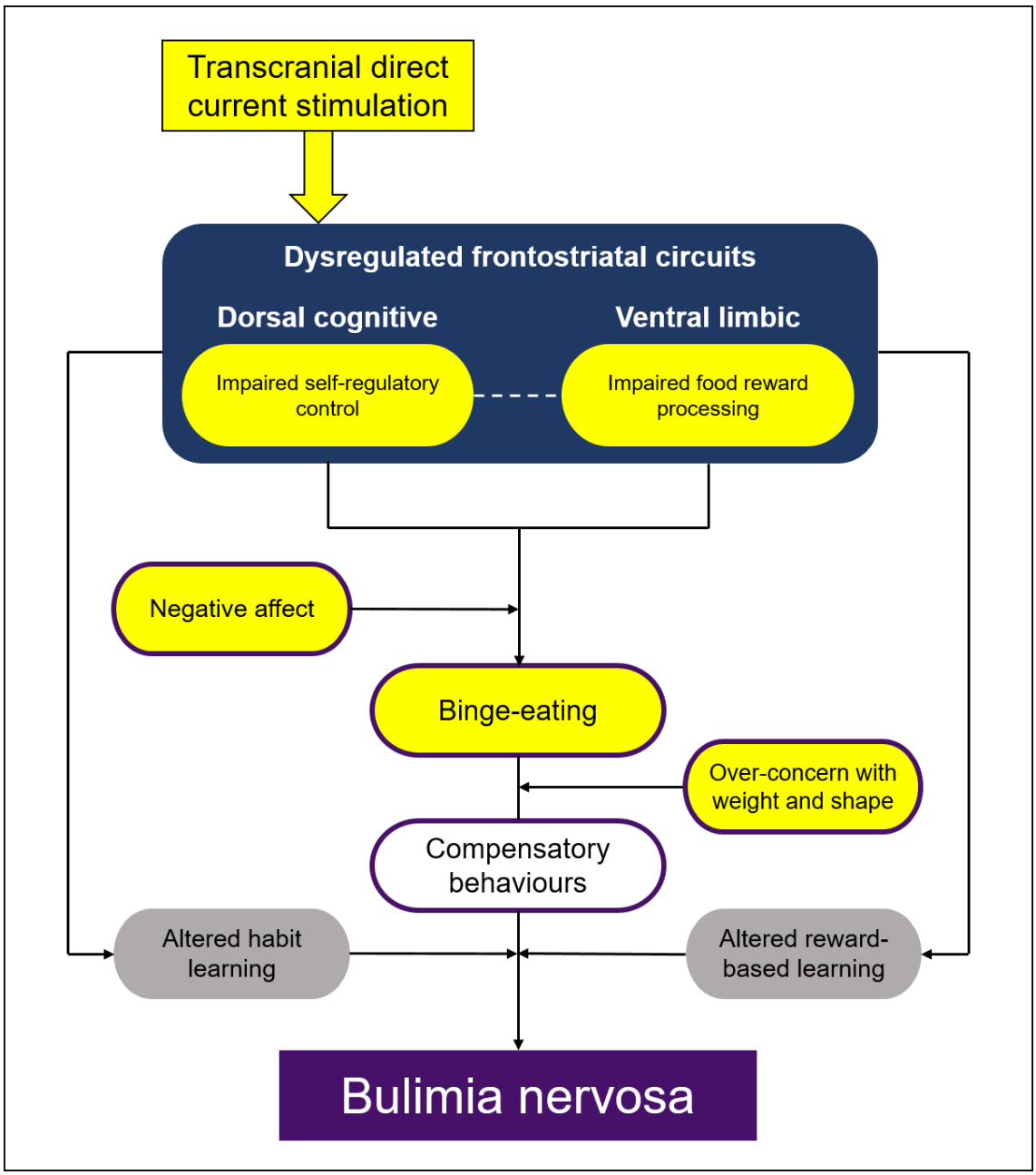


Figure 6.1 Neurobiological model of bulimia nervosa incorporating findings reported in this thesis.

Components influenced by transcranial direct current stimulation (tDCS) are shown in yellow. tDCS applied to the bilateral dorsolateral prefrontal cortex (part of the dorsal frontostriatal circuitry) was found to lower food craving (i.e., alter food reward processing) in healthy participants with frequent food cravings. It was also shown to decrease temporal discounting (i.e., improve self-regulatory control), and to reduce negative affect, the urge to binge-eat, and eating disorder cognitions (e.g., over-concern

with weight and shape[15]) in individuals with bulimia nervosa. Compensatory behaviours, habit learning, and reward-based learning were not assessed in either of the tDCS studies presented in this thesis.

6.4 STRENGTHS

The main strengths associated with the studies presented in this thesis relate to the novelty of the research conducted. Most notably, the paper that forms chapter 4 is the first to examine temporal discounting behaviour in people with BN, and chapter 5 reports on the first known investigation of tDCS in this patient population. The latter study was also innovative because, in addition to assessing the clinical efficacy of tDCS, it explored the impact of electrode polarity manipulation and probed the neurocognitive mechanisms driving the therapeutic response to stimulation. Although tDCS had been administered to 'frequent food cravers' prior to the experiment discussed in chapter 3, this was the first time the moderating role of self-regulatory control was considered. Finally, chapter 2 comprises the first published systematic review of tDCS across all psychiatric disorders to incorporate a standardised quality assessment.

[15] Eating disorder cognitions were assessed with the Mize's Eating Disorder Cognitions Questionnaire-Revised (MEDCQ-R). Although this questionnaire measures eating disorder cognitions in general, 16 of the 24 items relate to an over-concern with weight and shape.

6.5 LIMITATIONS

6.5.1 Methodological limitations

The major methodological limitations associated with the studies included in this thesis are outlined in the discussion sections of chapters 3-5. Overall, this research is primarily compromised by the assessment (or lack of assessment) of actual eating behaviour immediately following tDCS. Although food intake post-stimulation was measured among frequent food cravers, the task administered (see section 3.3.9) lacked ecological validity, which may explain why participants were found to eat equal amounts following real and sham stimulation. Indeed, a single session of tDCS applied to the bilateral DLPFC has previously been shown to reduce caloric ingestion in healthy individuals with frequent food cravings (Fregni et al., 2008). Due to validity concerns, and because laboratory eating paradigms are likely to elicit high levels of anxiety among individuals with EDs, the free-eating task was omitted from the BN tDCS study. Therefore, while the intervention significantly lowered the self-reported urge to binge-eat, whether this would have translated into an immediate reduction in actual binge-eating behaviour is unknown.

Additional shortcomings of the present research relate to the study samples. Firstly, due to safety concerns surrounding the delivery of tDCS in children (Kessler et al., 2013), only individuals over the age of 18 were eligible to participate. Since BN commonly begins in adolescence, and focus on the early pre-syndromal stages of illness may be associated with better outcomes in EDs (Currin & Schmidt, 2005), restricting tDCS interventions to adults with BN may reduce their probability of success. Secondly, of the 56 people who took part in the tDCS research, only 2 were male. Although BN affects more women than men, this ratio of male-to-female participants (1:27) far

exceeds sex ratio estimates for the disorder (see section 1.1.3.3). Thirdly, all 56 participants were educated to A-Level standard or higher, which to some extent may limit the generalisability of the findings. Nevertheless, while educational attainment among participants was higher than in the general population (in 2015 in England, 63.4% of 19-64-year-olds held a qualification at this level or above; Department for Education, 2017), being female and having BN have been associated with increased education (Kessler et al., 2014). Finally, the tDCS studies conducted are likely to have attracted an unrepresentative subgroup of patients with BN – i.e., those who have failed previous treatments and are thus interested in trying novel strategies – though this is an issue in most neuromodulation research that causes little concern since these brain-directed techniques are currently considered potential second-line therapies for psychiatric disorders.

6.5.2 Theoretical limitations

The rationale behind the present research stems partly from neurocircuit models of BN that implicate dysregulated dorsal and ventral frontostriatal pathways in the development of the disorder (see section 1.2.5). Whilst these models have provided valuable new insights into the pathophysiology of EDs, they fail to address cortical laterality and there are considerable inconsistencies and contradictions within the literature on which they are based. For example, functional magnetic resonance imaging investigations of reward system function in BN have observed hypo-activation (Radeloff et al., 2014), hyper-activation (Bohon & Stice, 2011), and 'normal' activation (Van den Eynde et al., 2013) in patients responding to food reward. Similarly, in comparison to healthy controls, individuals with BN have demonstrated both increased (Lock, Garrett, Beenhakker, & Reiss, 2011) and decreased (Marsh et al., 2009)

frontostriatal activation during neuropsychological tasks that engage self-regulatory control processes.

Inconsistencies in behavioural data also exist: although there is evidence that people with BN perform poorly on laboratory self-regulation tasks – including temporal discounting (see chapter 4) – many studies fail to replicate this finding (for reviews see Bartholdy, Dalton, O'Daly, Campbell, & Schmidt, 2016; Wu et al., 2016; Wu, Hartmann, Skunde, Herzog, & Friederich, 2013). Furthermore, 'controlled' dietary restraint may be just as central to BN as 'impulsive' binge-eating, and a relatively large proportion of individuals with the disorder have previously suffered from AN (Eddy et al., 2008), which is thought to involve excessive self-regulatory control (Steinglass et al., 2012). These poorly understood behavioural and neurobiological disparities thwart our understanding of the aetiology of BN and undermine the theoretical background to this research.

6.6 DIRECTIONS FOR FUTURE RESEARCH

6.6.1 Multi-session trials

Whilst the present research provides an important first step in elucidating the therapeutic utility of tDCS in BN, multi-session trials are needed to determine whether this neuromodulatory technique has potential for development as a treatment for the disorder. Indeed, the majority of tDCS clinical efficacy studies conducted in psychiatric populations have administered repeated sessions of stimulation (see chapter 2), which are presumed to have cumulative effects associated with greater magnitude and duration of behavioural responses, due to the induction of neuroplasticity (Brunoni et al., 2012; see section 1.3.3).

Empirical evidence for dose-dependent additivity in tDCS was reported by Monte-Silva and colleagues (2010), who found that performing a second stimulation session during the after-effects of a first led to a prolongation and enhancement of tDCS-induced effects. Furthermore, Boggio et al. (2007) observed enduring motor function improvement in stroke patients following five consecutive daily sessions of tDCS, but not after four weekly sessions. Although the optimal repetition rate and duration to promote tDCS-induced plasticity remains to be determined, long-lasting effects are undoubtedly crucial for clinical purposes (Brunoni et al., 2012), thus investigations of multi-session tDCS in BN are essential.

6.6.2 Accessibility considerations

The therapeutic utility of tDCS must be established through trials that are sufficiently powered and which include an adequate number of stimulation sessions (Charvet et al., 2015). As noted in section 2.5.3, additional evidence of efficacy from large-scale RCTs is necessary to permit the transition of this neuromodulatory technique from bench to bedside. Given that the effects of tDCS are cumulative, treatment protocols require multiple consecutive sessions spanning several weeks or months, which places a significant burden on patients and their caregivers, and often leads to high attrition rates (Charvet et al., 2015). Such demanding treatment regimens are likely to be problematic for individuals with BN, who are typically engaged in full- or part-time employment. Furthermore, these labour-intensive study designs are time-consuming and costly for the providers, particularly with increased sample sizes (Charvet et al., 2015).

In light of these difficulties, neuromodulation manufacturers have developed tDCS devices that enable controlled remote application and are specifically designed for

home-based use. While there has not yet been a clinical trial involving remotely-supervised tDCS in patients with a psychiatric disorder, protocols for those in neurological conditions are emerging (Kasschau et al., 2015; O'Neill, Sacco, & Nurmikko, 2015), and the safety and efficacy of a self-administered tDCS programme were recently established among patients with mal de debarquement syndrome (a neurological condition characterised by a persistent rocking or swaying sensation; Cha, Urbano, & Pariseau, 2016). Despite obvious limitations associated with self- or proxy-administered tDCS away from the clinic, the implementation of home-based tDCS in psychiatric research has the potential to dramatically accelerate progress in the field.

6.6.3 Transcranial direct current stimulation and cognitive training

Extensive data indicate that tDCS can enhance cognitive performance among people with mental disorders across a range of domains, including self-regulatory control (see chapter 5), working memory, attention, and processing speed (for a review see Tortella et al., 2015). There has therefore been growing interest in examining the potential synergistic effects of tDCS in combination with cognitive training (interventions designed to improve targeted cognitive abilities). For example, Saunders et al. (2015) treated a pilot group of patients suffering from post-traumatic stress disorder and poor working memory with computerised cognitive training and tDCS, and observed both behavioural and neuropsychological improvements in all four participants. Moreover, in individuals with major depression, the co-administration of cognitive control training and tDCS has been found to induce a greater reduction in symptoms than administration of either treatment in isolation (Brunoni et al., 2014; Segrave, Arnold, Hoy, & Fitzgerald, 2014). Since BN is associated with difficulties in various aspects of cognition (Van den Eynde et al., 2011; see chapter 4), and the therapeutic effects of tDCS in BN may be underpinned in part by alterations in self-regulatory control

processes (see chapter 5), the efficacy of combined tDCS and cognitive training in treating individuals with this condition certainly warrants investigation. Cognitive training methods that could be helpful here include attention bias modification, which targets cognitive biases such as those towards food cues, and mindfulness-based interventions, which work on building a present-focused attentional state that emphasises observing and experiencing. Both have shown promise in reducing binge-eating and other ED symptoms (Brockmeyer, Hahn, Reetz, Schmidt, & Friederich, 2015; Godfrey, Gallo, & Afari, 2015).

6.6.4 Transcranial direct current stimulation and neuroimaging

Despite numerous clinical applications in large numbers of patients suffering from psychiatric disorders, how tDCS influences the mentally affected human brain is not fully understood (Baeken, Brunelin, Duprat, & Vanderhasselt, 2016; see section 1.3.3). Indeed, the notion that the therapeutic effects of stimulation reported in the present research are underscored by changes in frontostriatal circuitry is speculative. Given that tDCS has poor spatial focality (Nitsche et al., 2007), it is possible that alterations within neighbouring circuits contributed to the responses observed.

In recent years, the simultaneous application of neuromodulation and neuroimaging methods has answered questions about the relationship between the physiological impact of tDCS and its behavioural consequences (Bestmann & Feredoes, 2013); however, so far, neuroimaging evidence of the distributed network modulatory effects of tDCS is largely limited to the motor system (Baeken et al., 2016). Future studies in psychiatric populations should use electroencephalography-recorded event related potentials to provide a fast indication of whether the neuronal network of interest has been targeted, while the co-registration of functional magnetic resonance imaging and

tDCS may help to elucidate spatial connectivity patterns following stimulation (Baeken et al., 2016). Finally, clinical trials that use neuroimaging to examine brain structure and function before and after multi-session tDCS interventions in BN and other mental disorders are merited.

6.6.5 Transcranial direct current stimulation and genetic testing

Data suggest that the individual genetic profile may modulate both the clinical (see section 2.5.1.1) and cognitive effects of tDCS. Of particular relevance to this research, a polymorphism of the catechol-O-methyltransferase (*COMT*) gene (Val158Met) – which regulates prefrontal dopamine – appears to predict the effect of tDCS to the left DLPFC on executive functions in healthy participants (Nieratschker, Kiefer, Giel, Krüger, & Plewnia, 2015; Plewnia et al., 2013). Specifically, *COMT* Met allele homozygosity (the high dopamine-activity genotype) has been associated with a deterioration of set-shifting ability (a measure of cognitive flexibility) following anodal tDCS (Plewnia et al., 2013), while Val homozygosity (the low dopamine-activity genotype) has been linked to a cathodal tDCS-induced impairment in response inhibition (a facet of self-regulatory control; Nieratschker et al., 2015). These findings have important implications for tDCS as a treatment for BN, since a therapeutic response in patients with the disorder may be dependent on improvements in self-regulatory control processes (see chapter 5). Importantly, there is evidence that homozygosity for the Val allele of the *COMT* Val158Met polymorphism increases the risk of having BN, and that patients with this genotype score higher on measures of ineffectiveness, drive for thinness, and perfectionism than those homozygous for the Met allele (Mikołajczyk, Grzywacz, & Samochowiec, 2010). Future research may benefit from accounting for genetic variability in the design and analysis of therapeutic tDCS applications

(Nieratschker et al., 2015), although the widespread implementation of this approach is unlikely to be economically or practically feasible.

6.6.6 Dimensional approaches to psychiatric disorders

The present research relies on a categorical diagnostic approach to BN, which considers the illness as being either present or absent. Although this model of classification has facilitated reliable clinical diagnosis and research in psychiatry for many years, it is increasingly being recognised as problematic for a number of reasons. For example, diagnostic categories based upon presenting signs and symptoms fail to align with findings emerging from clinical neuroscience and genetics, and the boundaries of these categories have not been predictive of treatment response (Insel et al., 2010). Moreover, this method of classification may fail to capture fundamental underlying mechanisms of dysfunction (Insel et al., 2010).

To address the need for a new approach to classifying mental disorders, the US National Institute of Mental Health (NIMH) launched the Research Domain Criteria (RDoC) project – a framework for organising research which incorporates an explicitly dimensional approach to psychopathology, and which will ultimately inform future taxonomic schemes (Cuthbert & Insel, 2013; Morris & Cuthbert, 2012). The RDoC framework is currently conceived as a two-dimensional matrix: the rows represent domains of functioning (e.g., cognitive systems) and the columns denote different levels of analysis (e.g, circuits) (Insel et al., 2010; National Institute of Mental Health, n.d.).

This approach is likely to guide the development of novel brain-directed treatments – like tDCS and other forms of neuromodulation – because it will make it possible to recruit participants to clinical trials based on a relevant neurobiological mechanism of

dysfunction, rather than simply enrolling individuals with a particular ‘disorder’. This may result in studies with samples spanning multiple *Diagnostic and Statistical Manual of Mental Disorders (DSM)* diagnoses. Indeed, the dysregulated frontostriatal circuits targeted in the present research have been implicated not only in BN, but also in several other conditions including AN, binge-eating disorder, and substance use disorders (see sections 1.2.6 and 1.2.7). Although RDoC is by no means a short-term project, it can be regarded as the first step towards bringing precision medicine to psychiatry (Insel, 2014).

6.7 CONCLUSIONS

The research presented in this thesis is based on the empirically supported premise that BN is underpinned by impairments in self-regulatory control and food reward processing, which are encoded in dorsal cognitive and ventral limbic frontostriatal circuits, respectively. According to this neurobiological model of BN, non-invasive brain stimulation techniques, such as tDCS, capable of enhancing frontostriatal function may hold promise as treatments for the disorder.

Taken together, the findings reported in chapters 2-5 provide preliminary support for the therapeutic utility of tDCS in BN. Firstly, the systematic review shows that this neuromodulatory tool has produced significant clinical benefits in a range of psychiatric disorders. Secondly, the RCT in healthy volunteers reveals that stimulation of the DLPFC with tDCS can reduce food craving (i.e., alter food reward processing). Thirdly, the cross-sectional study confirms the presence of self-regulatory control difficulties in patients with BN. Lastly, the RCT in BN demonstrates the ability of tDCS over the DLPFC to reduce symptoms, improve mood, and increase self-regulatory control

among individuals with the condition. Overall, this thesis paves the way for future research examining the potential tDCS treatment for BN.

6.8 REFERENCES

Baeken, C., Brunelin, J., Duprat, R., & Vanderhasselt, M.-A. (2016). The application of tDCS in psychiatric disorders: A brain imaging view. *Socioaffective Neuroscience & Psychology, 17(*6).

Bartholdy, S., Dalton, B., O'Daly, O. G., Campbell, I. C., & Schmidt, U. (2016). A systematic review of the relationship between eating, weight and inhibitory control using the stop signal task. *Neuroscience and Biobehavioral Reviews, 64*, 35-62.

Bestmann, S., & Feredoes, E. (2013). Combined neurostimulation and neuroimaging in cognitive neuroscience: Past, present, and future. *Annals of the New York Academy of Sciences, 1296*, 11-30.

Boggio, P. S., Nunes, A., Rigonatti, S. P., Nitsche, M. A., Pascual-Leone, A., & Fregni, F. (2007). Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients. *Restorative Neurology & Neuroscience, 25*(2), 123-129.

Bohon, C., & Stice, E. (2011). Reward abnormalities among women with full and subthreshold bulimia nervosa: A functional magnetic resonance imaging study. *International Journal of Eating Disorders, 44*(7), 585-595.

Brockmeyer, T., Hahn, C., Reetz, C., Schmidt, U., & Friederich, H.-C. (2015). Approach bias modification in food craving: A proof-of-concept study. *European Eating Disorders Review, 23*(5), 352-360.

Brunoni, A. R., Boggio, P. S., De Raedt, R., Bensenor, I. M., Lotufo, P. A., Namur, V., . . . Vanderhasselt, M. A. (2014). Cognitive control therapy and transcranial direct current stimulation for depression: A randomized, double-blinded, controlled trial. *Journal of Affective Disorders, 162*, 43-49.

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., . . . Fregni, F. (2012). Clinical research with transcranial direct current stimulation (tDCS): Challenges and future directions. *Brain Stimulation, 5*(3), 175-195.

Cha, Y.-H., Urbano, D., & Pariseau, N. (2016). Randomized single blind sham controlled trial of adjunctive home-based tDCS after rTMS for mal de debarquement syndrome: Safety, efficacy, and participant satisfaction assessment. *Brain Stimulation, 9*(4), 537-544.

Charvet, L. E., Kasschau, M., Datta, A., Knotkova, H., Stevens, M. C., Alonzo, A., . . . Bikson, M. (2015). Remotely-supervised transcranial direct current stimulation (tDCS) for clinical trials: Guidelines for technology and protocols. *Frontiers in Systems Neuroscience, 9*, 26.

Currin, L., & Schmidt, U. (2005). A critical analysis of the utility of an early intervention approach in the eating disorders. *Journal of Mental Health, 14*(6), 611-624.

Cuthbert, B. N., & Insel, T. R. (2013). Toward the future of psychiatric diagnosis: The seven pillars of RDoC. *BMC Medicine, 11*(1), 1-8.

Department for Education. (2017). *Further education and skills: January 2017 main tables - SFR07/2017*. Retrieved from https://www.gov.uk/government/statistics/further-education-and-skills-january-2017

Eddy, K. T., Dorer, D. J., Franko, D. L., Tahilani, K., Thompson-Brenner, H., & Herzog, D. B. (2008). Diagnostic crossover in anorexia nervosa and bulimia nervosa: Implications for DSM-V. *The American Journal of Psychiatry, 165*(2), 245-250.

Fregni, F., Orsati, F., Pedrosa, W., Fecteau, S., Tome, F. A., Nitsche, M. A., . . . Boggio, P. S. (2008). Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. *Appetite, 51*(1), 34-41.

Godfrey, K. M., Gallo, L. C., & Afari, N. (2015). Mindfulness-based interventions for binge eating: A systematic review and meta-analysis. *Journal of Behavioral Medicine, 38*(2), 348-362.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., . . . Wang, P. (2010). Research Domain Criteria (RDoC): Toward a new classification framework for research on mental disorders. *The American Journal of Psychiatry, 167*(7), 748-751.

Insel, T. R. (2014). The NIMH Research Domain Criteria (RDoC) project: Precision medicine for psychiatry. *The American Journal of Psychiatry, 171*(4), 395-397.

Kasschau, M., Sherman, K., Haider, L., Frontario, A., Shaw, M., Datta, A., . . . Charvet, L. (2015). A protocol for the use of remotely-supervised transcranial direct current stimulation (tDCS) in multiple sclerosis (MS). *Journal of Visualized Experiments*, 106, 53542.

Kessler, R. C., Shahly, V., Hudson, J. I., Supina, D., Berglund, P. A., Chiu, W. T., . . . Xavier, M. (2014). A comparative analysis of role attainment and impairment in binge-eating disorder and bulimia nervosa: Results from the WHO World Mental Health Surveys. *Epidemiology and psychiatric sciences, 23*(1), 27-41.

Kessler, S. K., Minhas, P., Woods, A. J., Rosen, A., Gorman, C., & Bikson, M. (2013). Dosage considerations for transcranial direct current stimulation in children: A computational modeling study. *PLOS ONE, 8*(9).

Lock, J., Garrett, A., Beenhakker, J., & Reiss, A. L. (2011). Aberrant brain activation during a response inhibition task in adolescent eating disorder subtypes. *The American Journal of Psychiatry, 168*(1), 55-64.

Marsh, R., Steinglass, J. E., Gerber, A. J., Graziano O'Leary, K., Wang, Z., Murphy, D., . . . Peterson, B. S. (2009). Deficient activity in the neural systems that mediate self-regulatory control in bulimia nervosa. *Archives of General Psychiatry, 66*(1), 51-63.

Mikołajczyk, E., Grzywacz, A., & Samochowiec, J. (2010). The association of catechol-O-methyltransferase genotype with the phenotype of women with eating disorders. *Brain Research, 1307*, 142-148.

Monte-Silva, K., Kuo, M.-F., Liebetanz, D., Paulus, W., & Nitsche, M. A. (2010). Shaping the optimal repetition interval for cathodal transcranial direct current stimulation (tDCS). *Journal of Neurophysiology, 103*(4), 1735.

Morris, S. E., & Cuthbert, B. N. (2012). Research Domain Criteria: Cognitive systems, neural circuits, and dimensions of behavior. *Dialogues in Clinical Neuroscience, 14*(1), 29-37.

National Institute of Mental Health. (n.d.). RDoC Matrix. Retrieved from https://www.nimh.nih.gov/research-priorities/rdoc/constructs/rdoc-matrix.shtml

Nieratschker, V., Kiefer, C., Giel, K., Krüger, R., & Plewnia, C. (2015). The COMT Val/Met polymorphism modulates effects of tDCS on response inhibition. *Brain Stimulation, 8*(2), 283-288.

Nitsche, M. A., Doemkes, S., Karaköse, T., Antal, A., Liebetanz, D., Lang, N., . . . Paulus, W. (2007). Shaping the effects of transcranial direct current stimulation of the human motor cortex. *Journal of Neurophysiology, 97*(4), 3109-3117.

O'Neill, F., Sacco, P., & Nurmikko, T. (2015). Evaluation of a home-based transcranial direct current stimulation (tDCS) treatment device for chronic pain: Study protocol for a randomised controlled trial. *Trials, 16*(1), 1-6.

Plewnia, C., Zwissler, B., Längst, I., Maurer, B., Giel, K., & Krüger, R. (2013). Effects of transcranial direct current stimulation (tDCS) on executive functions: Influence of COMT Val/Met polymorphism. *Cortex, 49*(7), 1801-1807.

Radeloff, D., Willmann, K., Otto, L., Lindner, M., Putnam, K., Leeuwen, S. V., . . . Wagner, A. (2014). High-fat taste challenge reveals altered striatal response in women recovered from bulimia nervosa: A pilot study. *World Journal of Biological Psychiatry, 15*(4), 307-316.

Saunders, N., Downham, R., Turman, B., Kropotov, J., Clark, R., Yumash, R., & Szatmary, A. (2015). Working memory training with tDCS improves behavioral and neurophysiological symptoms in pilot group with post-traumatic stress disorder (PTSD) and with poor working memory. *Neurocase, 21*(3), 271-278.

Segrave, R. A., Arnold, S., Hoy, K., & Fitzgerald, P. B. (2014). Concurrent cognitive control training augments the antidepressant efficacy of tDCS: A pilot study. *Brain Stimulation, 7*(2), 325-331.

Steinglass, J. E., Figner, B., Berkowitz, S., Simpson, H. B., Weber, E. U., & Walsh, B. T. (2012). Increased capacity to delay reward in anorexia nervosa. *Journal of the International Neuropsychological Society, 18*(04), 773-780.

Steinhausen, H. C., & Weber, S. (2009). The outcome of bulimia nervosa: Findings from one-quarter century of research. *The American Journal of Psychiatry, 166*(12), 1331-1341.

Tortella, G., Casati, R., Aparicio, L. V. M., Mantovani, A., Senço, N., D'Urso, G., . . . Brunoni, A. R. (2015). Transcranial direct current stimulation in psychiatric disorders. *World Journal of Psychiatry, 5*(1), 88-102.

Van den Eynde, F., Giampietro, V., Simmons, A., Uher, R., Andrew, C. M., Harvey, P.-O., . . . Schmidt, U. (2013). Brain responses to body image stimuli but not food are altered in women with bulimia nervosa. *BMC Psychiatry, 13*(1), 1-13.

Van den Eynde, F., Guillaume, S., Broadbent, H., Stahl, D., Campbell, I., Schmidt, U., & Tchanturia, K. (2011). Neurocognition in bulimic eating disorders: A systematic review. *Acta Psychiatrica Scandinavica, 124*(2), 120-140.

Wu, M., Brockmeyer, T., Hartmann, M., Skunde, M., Herzog, W., & Friederich, H.-C. (2016). Reward-related decision making in eating and weight disorders: A systematic review and meta-analysis of the evidence from neuropsychological studies. *Neuroscience and Biobehavioral Reviews, 61*, 177-196.

Wu, M., Hartmann, M., Skunde, M., Herzog, W., & Friederich, H.-C. (2013). Inhibitory control in bulimic-type eating disorders: A systematic review and meta-analysis. *PLOS ONE, 8*(12).

Appendices

LIST OF APPENDICES

APPENDIX A: PAPERS ASSOCIATED WITH THIS THESIS

Appendix A.1 Systematic review (chapter 2)

Journal of Psychiatric Research 74 (2016) 70–86

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Review article

A systematic review of the clinical efficacy of transcranial direct current stimulation (tDCS) in psychiatric disorders

Maria Kekic*, Elena Boysen [1], Iain C. Campbell, Ulrike Schmidt

Section of Eating Disorders, Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, 16 De Crespigny Park, London SE5 8AF, UK

ARTICLE INFO

Article history:
Received 24 August 2015
Received in revised form
17 December 2015
Accepted 18 December 2015

Keywords:
Transcranial direct current stimulation (tDCS)
Neuromodulation
Dorsolateral prefrontal cortex (DLPFC)
Depression
Schizophrenia
Substance use disorders (SUDs)

ABSTRACT

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique, which can be used to selectively disrupt patterns of neural activity that are associated with symptoms of mental illness. tDCS has been implemented in numerous therapeutic trials across a range of patient populations, with a rapidly increasing number of studies being published each year. This systematic review aimed to evaluate the efficacy of tDCS in the treatment of psychiatric disorders. Four electronic databases were searched from inception until December 2015 by two independent reviewers, and 66 eligible studies were identified. Depression was the most extensively researched condition, followed by schizophrenia and substance use disorders. Data on obsessive compulsive disorder, generalised anxiety disorder, and anorexia nervosa were also obtained. The quality of included studies was appraised using a standardised assessment framework, which yielded a median score corresponding to "weak" on the three-point scale. This improved to "moderate" when case reports/series were excluded from the analysis. Overall, data suggested that tDCS interventions comprising multiple sessions can ameliorate symptoms of several major psychiatric disorders, both acutely and in the long-term. Nevertheless, the tDCS field is still in its infancy, and several methodological and ethical issues must be addressed before clinical efficacy can truly be determined. Studies probing the mechanisms of action of tDCS and those facilitating the definition of optimised stimulation protocols are warranted. Furthermore, evidence from large-scale, multicentre randomised controlled trials is required if the transition of this therapy from the laboratory to the clinic is to be considered.

1. Introduction

Mental disorders constitute a major public health issue, directly accounting for 7.4% of disease burden worldwide (Murray et al., 2012) and 17.8% in the European Union (Wittchen et al., 2011). They are the leading cause of years lived with disability globally (Whiteford et al., 2013), impacting personal well-being, social relationships and work productivity, and are associated with substantial loss of quality of life (Alonso et al., 2004). Despite an increase in the rate of treatment, psychiatric morbidity has remained relatively stable over the past two decades (Kessler et al., 2005; Wittchen et al., 2011), thus there is a need to develop novel therapeutic strategies to improve clinical outcomes.

Recent advances in functional neuroimaging have facilitated an improved understanding of the disturbances in neural circuitry that underlie mental disorders (Frangou, 2014; Price and Drevets, 2013). Consequently, there has been increased interest in neuromodulation methods which can be used to selectively disrupt patterns of neural activity that are associated with symptoms of illness, with the objective of improving behavioural outcomes whilst generating information about disease mechanisms. These emerging brain-directed interventions adhere to an experimental therapeutics approach, which is now widely regarded as the gold-standard strategy for treatment-focused psychiatric research (Insel, 2014; Insel and Gogtay, 2014; Medical Research Council, 2010).

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique which delivers low-amplitude direct currents to the brain via two surface sponge electrodes (anode and cathode) attached to distinct areas of the scalp with a rubber

* Corresponding author.
E-mail addresses: maria.kekic@kcl.ac.uk (M. Kekic), elena.boysen@student.uni-tuebingen.de (E. Boysen), iain.campbell@kcl.ac.uk (I.C. Campbell), ulrike.schmidt@kcl.ac.uk (U. Schmidt).
[1] Present address: Department of Psychosomatic Medicine and Psychotherapy, Medical University Hospital Tübingen, Osianderstr. 5, 72076 Tübingen, Germany.

http://dx.doi.org/10.1016/j.jpsychires.2015.12.018
0022-3956/

headband (Wagner et al., 2007). The current penetrates the skull and enters the brain from the anode, travels through the tissue, and exits via the cathode (George and Aston-Jones, 2010). tDCS presents several practical advantages over alternative neuromodulation modalities – it has a favourable safety-feasibility profile, offers a convincing placebo, can be applied bilaterally, and is portable and inexpensive.

During the past decade, tDCS has been implemented in numerous trials across a range of patient populations and psychiatric conditions, with a rapidly increasing number of studies being published each year (Fig. 1). This systematic review critically evaluates the clinical efficacy of tDCS in people with mental illness, and is warranted given the limited efficacy of existing therapies, the evidence that psychiatric disorders are neural circuit-based disorders that could benefit from brain-directed interventions, and the appealing characteristics of tDCS in comparison to other forms of neuromodulation. Although several reviews and meta-analyses have previously addressed this topic, the majority have either studied major depression (Berlim et al., 2013; Brunoni et al., 2012a; Kalu et al., 2012; Meron et al., 2015; Shiozawa et al., 2014d) or schizophrenia alone (Mondino et al., 2015c), or used unsystematic search procedures (Brunoni et al., 2012b; Kuo et al., 2014; Tortella et al., 2015) which promote a number of biases (Schmidt and Gotzsche, 2005). To our knowledge, one prior publication has systematically reviewed the therapeutic effects of tDCS across all psychiatric disorders (Mondino et al., 2014). Given the high growth rate of publication in the field, we have provided an up-to-date and comprehensive synthesis of the full evidence base, which is inclusive of all psychiatric conditions and study designs, and which uses a standardised quality assessment.

2. Material and methods

2.1. Selection criteria

Studies in English of any design that investigated the clinical efficacy of tDCS in individuals with psychiatric disorders were eligible for inclusion. Studies of participants with neurological conditions were excluded, as were those that did not report any symptom outcome variables. Publications were not restricted based on whether details of a Diagnostic and Statistical Manual of Mental Disorders/International Classification of Diseases diagnosis were given, and those involving co-interventions were eligible for inclusion if the effects of tDCS *per se* were discernible.

2.2. Search strategy

Four electronic databases (MEDLINE, Embase, PsycINFO, and CINAHL) were searched (via OvidSP and EBSCOhost) from inception until 3rd December 2015 using the following Medical Subject Headings and keywords: transcranial direct current stimulation, tDCS, and transcranial DC stimulation, in combination with mental disorder, mental illness, psychiatric disorder, psychiatric disease, addict*, anorexi*, anxiety disorder, auditory verbal hallucinations, bipolar disorder, bulimi*, catatonia, craving, dependence, depersonali?ation, depressi*, eating disorder, mania, obsessive compulsive disorder, OCD, panic disorder, personality disorder, phobi*, posttraumatic stress disorder, psychosis, PTSD, and schizophrenia. These searches were supplemented by internet searches and handsearches of reference lists of relevant papers and reviews. Citation tracking in Web of Science was also performed.

Titles and abstracts of retrieved publications were imported into EndNote, duplicates were removed, and papers that were deemed highly unlikely to be relevant were disregarded. Full-text versions of the remaining articles were then obtained and screened according to the pre-specified eligibility criteria. All papers that did not meet the inclusion criteria were excluded, with the reasons

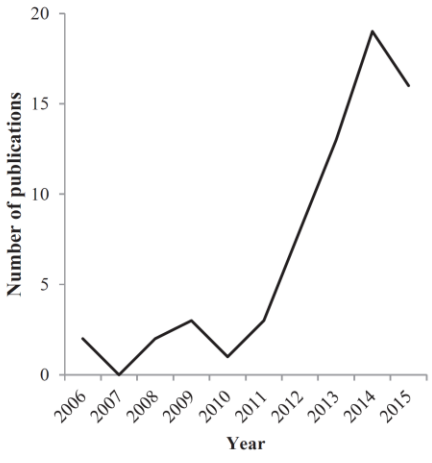


Fig. 1. Number of publications included in this review by year between 2006 and 2015. Note: databases were searched for papers published online or in print until 3rd December 2015.

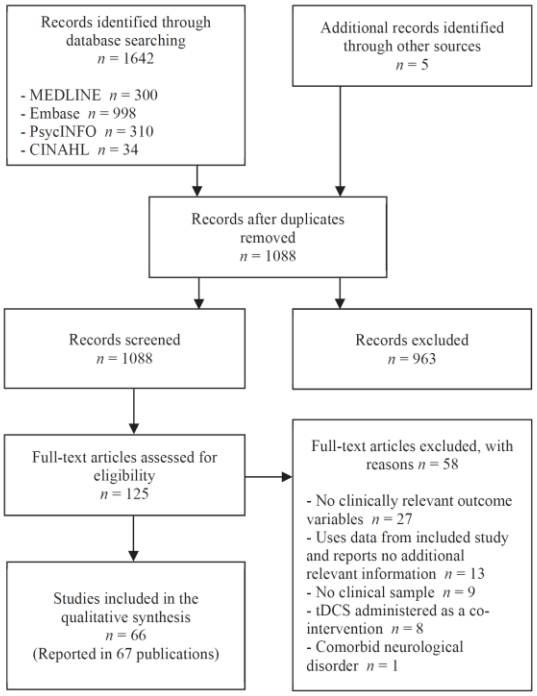


Fig. 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

documented (Fig. 2). The entire search process was conducted independently by two reviewers (M.K. and E.B.) and disagreements at the final stage were resolved by consensus.

2.3. Quality assessment and data extraction

The quality of included studies was appraised using a standardised evaluation framework – the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies (Thomas et al., 2004) – which is suitable for use with multiple study designs. The instrument assesses six methodological domains: selection bias, study design, confounders, blinding, data collection methods, and withdrawals and dropouts. Each component is rated as strong, moderate, or weak on a three-point scale and these scores are averaged to provide a global rating. The quality assessment was performed independently by two reviewers (M.K. and E.B.) and discrepancies were discussed until an agreement was reached.

The principal reviewer (M.K.) extracted data from all included studies into an electronic summary table which was then checked by another reviewer (E.B.). Information collected related to patient population, sample size, study design, stimulation protocol, measurement of clinical efficacy, and relevant findings. Due to the methodological diversity of the included studies, a narrative synthesis is presented.

3. Results

3.1. Characteristics of included studies

We identified 66 studies (reported in 67 publications, including data from 1021 participants) that met the inclusion criteria for this review (Fig. 2). The majority (30 studies) evaluated the efficacy of tDCS for the treatment of major depression in patients with major depressive disorder (MDD) or bipolar disorder (BP). The remaining studies were of patients with schizophrenia (23 studies), substance use disorders (SUDs; 7 studies), obsessive compulsive disorder (OCD; 4 studies), generalised anxiety disorder (GAD; 1 study), and anorexia nervosa (AN; 1 study). There were 23 randomised controlled trials (RCTs) and 41 open-label studies (2 had blind-raters) including 24 case reports/series. In addition, there was one double-blind, sham-controlled case report and one study with a hybrid design involving both double-blind, sham-controlled and open-label conditions. All studies had adult-only samples which differed substantially in size, ranging from 1 to 120 participants ($M = 18.09$, $SD = 19.99$).

All but four of the studies had stimulation protocols comprising multiple sessions; however, the duration, number, and frequency of these sessions, as well as the tDCS parameters employed, varied considerably across trials (Tables 2–5). The unilateral or bilateral dorsolateral prefrontal cortex (DLPFC) was targeted in 59 of the 66 studies. Other hypothesis-driven sites of stimulation were the temporoparietal junction (TPJ), cerebellum, occipital lobe, orbitofrontal cortex (OFC), frontotemporal region, pre-supplementary and supplementary motor areas (pre-SMA/SMA), and Wernicke's area.

3.2. Quality of included studies

The median global rating derived from the EPHPP Quality Assessment Tool for Quantitative Studies was 3 (weak). Overall, the weakest scores were obtained for the selection bias component of the tool because 38% of studies were case reports/series and a further 26% did not adequately describe the participant selection process. A high number of weak ratings were also assigned for the blinding component because 62% of the studies were open-label. The strongest-scoring dimension was data collection methods because 63 of the 66 studies used at least one standardised outcome measure with known reliability and validity. Where relevant, withdrawals and dropouts were generally addressed and reported accurately, and only 5 studies had a retention rate lower than 80% at the final stage of data collection. Of the 18 studies that involved 2 or more independent experimental groups, 16 reported no baseline between-group differences with respect to important variables, 1 noted that the active group had more severe symptoms pre-tDCS, and 1 study did not provide this information. A numerical summary of the component ratings is provided in Table 1. Since the high proportion of case reports/series notably impacted the results of the quality assessment, average scores were calculated with and without these studies included.

3.3. Study findings

3.3.1. Major depression

A number of studies have provided evidence that unilateral DLPFC stimulation (anodal tDCS to the left DLPFC [l-DLPFC], cathodal tDCS to a contralateral intra- or extra-cephalic region) can ameliorate symptoms of major depression (Table 2). The earliest of these were conducted by Fregni and colleagues (Fregni et al., 2006a, 2006b) who found that five sessions of sham-controlled tDCS induced significant improvements in mood (indexed by the Hamilton Rating Scale for Depression [HRSD] and the Beck Depression Inventory [BDI]) in two small samples of MDD patients ($N = 10$, $N = 18$). Their findings were later extended by Boggio et al. (2008a) who demonstrated that, in 40 MDD patients, 10 sessions of anodal tDCS to the l-DLPFC led to persisting reductions in HRSD and BDI scores when compared with both sham tDCS and an active control (anodal tDCS to the occipital cortex). Lasting improvements in depressive symptoms following 10 sessions of anodal l-DLPFC tDCS were also recorded in 8 HIV-MDD co-diagnosed individuals (Knotkova et al., 2012) and one 92-year-old MDD patient (Shiozawa et al., 2014a).

Other studies of anodal tDCS to the l-DLPFC in major depression have yielded less encouraging results. For example, Palm et al. (2009) reported that 16 sessions of tDCS did not exert a meaningful therapeutic effect in a patient with treatment-resistant MDD, and Wolkenstein and Plewnia (2013) recorded no tDCS-related changes in positive or negative affect (indexed by the Positive and Negative Affect Schedule [PANAS]) in 22 MDD patients following real versus sham tDCS (though a single session protocol was used). More ambiguous findings have also been documented: a 2-week course of sham-controlled tDCS had no effect on clinical

Table 1
Median and mean component ratings from the EPHPP Quality Assessment Tool for Quantitative Studies.

Component	Ratings			
	All included studies ($N = 66$)		Excluding case reports/series ($n = 41$)	
	Median	Mean	Median	Mean
Selection bias	3	2.65	2	2.44
Study design	2	2.05	1	1.44
Confounders	1	1.21	1	1.21
Blinding	3	2.24	1	1.83
Data collection methods	1	1.08	1	1.12
Withdrawals and dropouts	1	1.23	1	1.23
Global rating	3	2.35	2	1.93

Ratings: 1 = strong; 2 = moderate; 3 = weak.

Table 2
Studies in patients with major depression (in chronological order).

Study	N[a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
Fregni et al. (2006a)	10	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supraorbital area	1	35	20 min, 5 sessions (1 per day for 5 alternate days)	HRSD, BDI	Improvement in depressive symptoms after active versus sham tDCS.	No mention of DSM/ICD diagnosis.
Fregni et al. (2006b)	18	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supraorbital area	1	35	20 min, 5 sessions (1 per day for 5 alternate days)	HRSD	Improvement in depressive symptoms after active versus sham tDCS.	No mention of DSM/ICD diagnosis.
Boggio et al. (2008a)	40	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS of the DLPFC; (ii) tDCS of the occipital cortex (active control); (iii) sham tDCS	Left DLPFC	Right supraorbital area	2	–	20 min, 10 sessions (1 per weekday for 2 consecutive weeks)	HRSD-21, BDI	Improvement in depressive symptoms after tDCS to the DLPFC versus sham tDCS and tDCS to the occipital cortex, maintained for at least 1 month.	
Ferrucci et al. (2009b)	14	MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	32	20 min, 10 sessions (2 per day for 5 consecutive days)	BDI, HRSD, self-reported mood (VAS)	Improvement in depressive symptoms post-tDCS, maintained for at least 1 month.	
Ferrucci et al. (2009a)	32	MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	–	20 min, 10 sessions (2 per day for 5 consecutive days)	HRSD, BDI	Improvement in depressive symptoms post-tDCS, particularly in patients with severe depression who maintained improvements for at least 1 month.	
Palm et al. (2009)	1	MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right supraorbital area	1	35	20 min, 16 sessions (1 per day then 2 per day over 27 days)	BDI, HRSD, CGI	Improvement in depressive symptoms post-tDCS, but no change in CGI score.	
Loo et al. (2010)	35	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right lateral orbit	1	35	20 min, 5 sessions (1 per day for 5 alternate weekdays) plus 5 further sessions (active for both groups) at the same treatment frequency	MADRS, HRSD, CGI-S, BDI, PGI-I	No improvement in depressive symptoms after active versus sham tDCS.	Sessions 6–10 were active for all participants, but they were not made aware of this until the blind was broken. Those who received 5 sham sessions initially were offered the opportunity to receive 5 further active sessions.
Brunoni et al. (2011b)	31	MDD and BP	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	35	20 min, 10 sessions (2 per day for 5 consecutive days)	HRSD, BDI	Improvement in depressive symptoms post-tDCS, maintained for at least 1 month. Depression severity was positively related with symptom improvement.	
Martin et al. (2011)	11	MDD and BP	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right upper arm	2	35 (100 for extracephalic electrode)	20 min, 20 sessions (1 per weekday for 4 consecutive weeks)	MADRS, IDS, CGI-S, QIDS-SR, MADRS-SR	Improvement in depressive symptoms post-tDCS.	Participants were non-responders or relapsers from Loo et al. (2012).
Blumberger et al. (2012)	24	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right DLPFC	2	35	20 min, 15 sessions (1 per weekday for 3 consecutive weeks)	HRSD, MADRS, BPRS, BDI-II	No improvement in depressive symptoms after active versus sham tDCS.	

(*continued on next page*)

Table 2 (*continued*)

Study	N[a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
Dell'Osso et al. (2012)	23	MDD and BP	Open-label, blind-rater, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	32	20 min, 10 sessions (2 per day for 5 consecutive days)	MADRS, HRSD	Improvement in depressive symptoms post-tDCS, maintained for at least 1 week.	
Knotkova et al. (2012)	8	MDD (co-diagnosed HIV)	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right supraorbital area	2	25	20 min, 10 sessions (1 per weekday for 2 consecutive weeks)	HRSD, MADRS	Improvement in depressive symptoms post-tDCS, maintained for at least 2 weeks (further improvement in MADRS scores only).	No mention of DSM/ICD diagnosis.
Loo et al. (2012) *[Phase I]*	58	MDD and BP	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right lateral orbit	2	35	20 min, 15 sessions (1 per weekday for 3 consecutive weeks)	MADRS, IDS, CGI-S, QIDS-C, QIDS-SR	Improvement in depressive symptoms (MADRS scores only) after active versus sham tDCS, but an equal number of participants in each group met the criterion for response and no participants met the criterion for remission.	
Loo et al. (2012) *[Phase II]*	52	MDD and BP	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right lateral orbit	2	35	20 min, 15 sessions (1 per weekday for 3 consecutive weeks) then additional weekly sessions for 1-month (responders only)	MADRS, IDS, CGI-S, QIDS-C, QIDS-SR	27 participants Met the criterion for response post-tDCS. There were 22 and 20 responders at 1-week and 1-month follow-ups, respectively.	Participants previously received active or sham tDCS in phase I of the trial (Loo et al., 2012). The group who received active tDCS in phase I had better responder rates after phase II.
Palm et al. (2012)	22	MDD and BP	Randomised, double-blind, sham-controlled, crossover	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supraorbital area	1 or 2	35	20 min, 10 sessions (1 per weekday for 2 consecutive weeks)	HRSD, PANAS, BDI	No improvement in clinical depression ratings, but increase in subjectively reported positive emotions (PANAS), after active versus sham tDCS.	
Alonzo et al. (2013)	64	MDD and BP	Exploratory analysis of Loo et al. (2012)		No tDCS performed					MADRS	Improvement in dysphoria and retardation after active versus sham tDCS.	Used Loo et al. (2012) dataset.
Brunoni et al. (2013a)	82	MDD and BP (BP-II and BP-NOS only)	Open-label, blind-rater, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	35	20 min, 10 sessions (2 per day for 5 consecutive days)	HRSD, BDI	Improvement in depressive symptoms post-tDCS. Use of benzodiazepines was associated with a worse outcome.	
Brunoni et al. (2013b) *[Phase I SELECT-TDCS]*	103	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS + placebo pill; (ii) sham tDCS + sertraline; (iii) tDCS + sertraline; (iv) sham tDCS + placebo pill	Left DLPFC	Right DLPFC	2	25	30 min, 12 sessions (1 per weekday for 2 consecutive weeks then 1 per week for 2 alternate weeks)	MADRS, HRSD, CGI-S, BDI	Improvement in depressive symptoms after active versus sham tDCS. Greatest effects after combined tDCS/sertraline treatment, maintained for at least 2 weeks.	
D'Urso et al. (2013)	1	MDD	Open-label, uncontrolled	(i) tDCS; (ii) tDCS + CBT	Left DLPFC	Right DLPFC	1.5	–	10 sessions (1 per weekday for 2 consecutive weeks) x 2	HRSD	Improvement in depressive symptoms post-tDCS, only partially maintained over the 4-week follow-up period. The combined treatment induced acute improvements and complete remission of symptoms at 12-month follow-up.	CBT sessions were performed weekly during tDCS treatment and throughout the following 6 months.
Martin et al. (2013)	26	MDD and BP	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right lateral orbit or right upper arm	2	35 (100 for extracephalic electrode)	20 min (1 per week for 3 consecutive months then 1 per fortnight for 3 consecutive months)	MADRS, relapse rates	After tDCS, half the sample survived for at least 24 weeks without relapse.	Participants were from Loo et al. (2012) or Martin et al. (2011). Three participants commenced a new antidepressant treatment during the study.

Valiengo et al. (2013) *[Phase II SELECT-TDCS]*	23	MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	25	30 min, 10 sessions (1 per weekday for 2 consecutive weeks)	MADRS	Improvement in depressive symptoms post-tDCS.	Participants were non-responders who received sham tDCS in phase I of SELECT-TDCS (Brunoni et al., 2013b).
Valiengo et al. (2013) *[Phase III SELECT-TDCS]*	42	MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	25	30 min, 9 sessions (1 per week for 6 alternative weeks then 1 per month for 3 consecutive months)	MADRS relapse rates	After tDCS, half the sample survived for at least 24 weeks without relapse. The mean response duration was 11.7 weeks.	Participants were responders who received active tDCS in phase I or phase II of SELECT-TDCS (Brunoni et al., 2013b; Valiengo et al., 2013).
Wolkenstein and Plewnia (2013)	22	MDD	Randomised, double-blind, sham-controlled, crossover	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right deltoid	1	35	20 min, 1 session	PANAS	No change in subjective mood state after active versus sham tDCS.	
Brunoni et al. (2014a)	37	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS + CCT; (ii) sham tDCS + CCT	Left DLPFC	Right DLPFC	2	25	30 min, 10 sessions (1 per weekday for 2 consecutive weeks)	HRSD, BDI	Both groups showed similar improvement in depressive symptoms after treatment. Active tDCS + CCT was not superior to sham tDCS + CCT.	
Brunoni et al. (2014b)	120	MDD	Exploratory analysis of Brunoni et al. (2013b)		No tDCS performed					MADRS	Improvement in concentration difficulties, pessimistic thoughts, and suicidal thoughts after active versus sham tDCS.	Used Brunoni et al. (2013b) dataset.
Dell'Osso et al. (2014)	23	MDD and BP	Follow-up of Dell'Osso et al. (2012), blind-rater		No tDCS performed					MADRS, HRSD	Improvement in depressive symptoms post-tDCS, maintained for at least 3 months in half the sample.	Participants were from Dell'Osso et al. (2012).
Ho et al. (2014)	14	MDD	Open-label, uncontrolled	(i) Fronto-occipital tDCS; (ii) fronto-cerebellar tDCS	Left supraorbital area	(i) Bilateral occipital lobe; (ii) bilateral cerebellum	2	35 (100/50 for cathodes)	20 min, 20 sessions (1 per weekday for 4 consecutive weeks)	MADRS	Improvement in depressive symptoms after fronto-occipital tDCS only.	
Player et al. (2014)	18	MDD and BP-II	Double-blind, sham-controlled ($n = 6$); open-label, uncontrolled ($n = 12$)	(i) tDCS; (ii) sham tDCS ($n = 6$)	Left DLPFC	Right frontal area, right upper arm, or occipital-cerebellar region	2–2.5	–	20-30 min, 13–21 sessions (consecutive weekdays)	MADRS	Improvement in depressive symptoms after sham tDCS, but greater improvement after active tDCS.	Participants were from several different trials which varied in study design/tDCS parameters. Clinical results from one subject were also reported in Loo et al. (2012).
Segrave et al. (2014)	27	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS + CCT; (ii) sham tDCS + CCT; (iii) tDCS + sham CCT	Left DLPFC	Right lateral orbit	2	35	24 min, 5 sessions (1 per day for 5 consecutive days)	MADRS, BDI-II	Improvement in depressive symptoms post-tDCS, partially maintained for at least 3 weeks (BDI-II scores only). Combined tDCS/CCT treatment was most effective but had a delayed benefit.	
Shiozawa et al. (2014a)	1	MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right deltoid	2	–	30 min, 10 sessions (1 per weekday for 2 consecutive weeks)	HRSD	Improvement in depressive symptoms post-tDCS, maintained for at least 3 weeks.	No mention of DSM/ICD diagnosis.
Bennabi et al. (2015)	23	MDD	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supraorbital area	2	35	30 min, 10 sessions (2 per day for 5 consecutive days)	HRSD, MADRS, BDI	No improvement in depressive symptoms after active versus sham tDCS, but more participants in the active group met the response and remission criteria immediately, 12 days, and 30 days after treatment.	

(*continued on next page*)

Table 2 (*continued*)

Study	N[a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
Ho et al. (2015)	4	MDD	Open-label, uncontrolled	(i) tDCS	Left fronto-temporal region	Right fronto-temporal region	2.5	35/16	30 min, 20 sessions (1 per weekday for 4 consecutive weeks)	MADRS	Improvement in depressive symptoms after tDCS. At the end of treatment, two participants met the criteria for response and one met the criteria for remission.	Participants had previously received multiple courses of tDCS (Chan et al., 2013; Loo et al., 2012; Martin et al., 2011, and unpublished data).
Shiozawa et al. (2015)	1	MDD	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right DLPFC	2	35	20 min, 5 sessions (1 per day for 5 consecutive days)	HRSD	Intensification of depressive symptoms after tDCS.	No mention of DSM/ICD diagnosis. Patient had right hemispheric dominance (he was left-handed and was diagnosed with dyslexia during childhood).

BDI, Beck Depression Inventory; BDI-II, Beck Depression Inventory-II; BP, bipolar disorder; BP-II, bipolar II disorder; BP-NOS, bipolar disorder not otherwise specified; BPRS, Brief Psychiatric Rating Scale; CCT, cognitive control training; CGI, Clinical Global Impression; CGI-S, Clinical Global Impression - Severity scale; DLPFC, dorsolateral prefrontal cortex; DSM, Diagnostic and Statistical Manual of Mental Disorders; HRSD, Hamilton Rating Scale for Depression; ICD, International Classification of Diseases; IDS, Inventory of Depressive Symptomatology; MADRS, Montgomery–Åsberg Depression Rating Scale; MADRS-SR, Montgomery–Åsberg Depression Rating Scale - Self-Report; MDD, major depressive disorder; PANAS, Positive and Negative Affect Schedule; PGI-I, Patient Global Impression of Improvement; QIDS-C, Quick Inventory of Depressive Symptomatology - Clinician Rating; QIDS-SR, Quick Inventory of Depressive Symptomatology - Self-Report; SELECT-TDCS, The sertraline versus electrical current therapy for treating depression clinical study; tDCS, transcranial direct current stimulation; VAS, visual analogue scale.

[a] *N* refers to the number of participants whose data was included at the final stage of analysis.

depression ratings (HRSD, BDI) but increased subjectively-rated positive emotions (according to the PANAS) in 22 participants with refractory MDD ($n = 20$) or BP ($n = 2$) (Palm et al., 2012). Similarly, whilst 10 sessions of sham-controlled twice-daily tDCS did not alleviate symptoms in 23 patients with treatment-resistant MDD (indexed by the HRSD, BDI, and Montgomery-Åsberg Depression Rating Scale [MADRS]), more participants in the active tDCS group met the response and remission criteria immediately, 12 days, and 30 days after treatment (Bennabi et al., 2015).

In a parallel group RCT conducted by Loo et al. (2010), comparable reductions in depression severity (HRSD, MADRS) occurred following 5 sessions of real and sham anodal l-DLPFC tDCS in 35 patients with MDD. Although the authors later recorded a reduction in MADRS scores in 58 MDD/BP patients following 15 sessions of sham-controlled tDCS, this result was clinically modest, the differences did not reach significance on any other mood outcome measures, and an equal number of participants in the active and sham groups met the response and remission criteria (Loo et al., 2012). Nevertheless, a between-group difference in the proportion of responders became apparent after participants ($n = 52$) received an additional 15 sessions of open-label active tDCS: at 1-week and 1-month follow-ups, responder rates were superior in the group that had received active treatment throughout (Loo et al., 2012). Interestingly, 11 participants who showed an inadequate response to, or relapsed following, 3 weeks of active tDCS treatment in this study (Loo et al., 2012) subsequently displayed moderate clinical improvements after 20 further sessions of open-label tDCS in which the cathode was placed extracephalically (over the right upper arm) instead of over the right lateral orbit (Martin et al., 2011). Those who met the criterion for response ($n = 7$), and 19 responders from the original study (Loo et al., 2012), then received 6 months of weekly/fortnightly continuation tDCS and data indicated that the cumulative probability of surviving without relapse was 84% at 3 months and 51% at 6 months (Martin et al., 2013).

In contrast to those described above, a number of studies investigating the effects of tDCS in major depression have used bilateral DLPFC modulation (anodal left/cathodal right). For example, Ferrucci et al. (2009b) administered 10 sessions of twice-daily open-label tDCS to 14 patients with severe, drug-resistant MDD and observed mood improvements (HRSD, BDI, self-report visual analogue scales [VASs]) which persisted for at least 1 month after the end of treatment. Similarly, Dell'Osso et al. (2012) delivered tDCS at the same parameters to 23 poor-responder depressed patients (MDD = 15, BP = 8) and noted a clinical benefit that was maintained for at least 3 months in half of the sample (Dell'Osso et al., 2014). This protocol (10 sessions of twice-daily open-label tDCS) was adopted by three further studies which explored the comparative benefits of tDCS in patients with differing clinical profiles (Brunoni et al., 2013a, 2011b; Ferrucci et al., 2009a). Robust and persisting improvements in depressive symptoms were recorded across a total of 145 individuals with MDD ($n = 112$) or BP ($n = 33$) (Brunoni et al., 2013a, 2011b; Ferrucci et al., 2009a), and whilst the treatment appeared to be equally effective for patients regardless of their diagnosis (Brunoni et al., 2013a, 2011b), a better response was seen in participants with severe MDD than in those with mild/moderate MDD (Ferrucci et al., 2009a). Interactions between tDCS and drug therapy were also reported: whereas benzodiazepine use was associated with a worse outcome, antidepressants generally increased the beneficial effects of tDCS (Brunoni et al., 2013a).

Evidence from a multi-phase trial by Brunoni et al. (2013b) supports the finding that bilateral DLPFC tDCS has greater efficacy when administered with antidepressants. During phase I, 120 patients with MDD were assigned to 1 of 4 groups: sham tDCS/placebo pill (placebo), sham tDCS/sertraline (sertraline-only), active

Table 3 (*continued*)

Study	N[a]	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
		Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
Nawani et al. (2014b)		Open-label, uncontrolled						20 min, 10 sessions (2 per day for 5 consecutive days)		Reduction in AVH post-tDCS.	
Shiozawa et al. (2014c)	1	Open-label, uncontrolled	(i) tDCS	Left TPJ	Right TPJ	2	35	20 min, 10 sessions (1 per day for 10 consecutive days)	PANSS	No improvement in schizophrenic symptoms post-tDCS.	No mention of DSM/ICD diagnosis.
Shivakumar et al. (2014)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	–	20 min, 10 sessions (2 per day for 5 consecutive days) plus 6 intermittent booster sessions over 1 year (2 per day, single day)	PSYRATS (AHS)	Complete cessation of AVH after acute course of tDCS, maintained for 3 months. Booster tDCS sessions controlled 3 subsequent relapses over 1 year. Participant was free of AVH at 1-year follow-up.	
Bose et al. (2015)	1	Open-label, uncontrolled	(i) left-sided tDCS; (ii) right-sided tDCS	(i) Left DLPFC; (ii) right DLPFC	(i) Left TPJ; (ii) right TPJ	2	35	(i) 20 min, 18 sessions (2 per day for 9 consecutive days); (ii) 20 min, 20 sessions (2 per day for 10 consecutive days)	PSYRATS (AHS)	No improvement in schizophrenic symptoms after left-sided tDCS, but reduction in AH after right-sided tDCS.	Electrode positioning was modified due to lack of clinical response.
Brunelin et al. (2015)	16	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	35	20 min, 10 sessions (frequency not stated)	AHRS	Reduction in AH post-tDCS.	Patients with a comorbid tobacco use disorder ($n = 10$) were less responsive to tDCS.
Gomes et al. (2015)	15	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right DLPFC	2	–	20 min, 10 sessions (1 per weekday for 2 consecutive weeks)	PANSS	Improvement in negative but not positive symptoms after active versus sham tDCS.	At baseline, the tDCS group had higher PANSS scores for the positive scale relative to the sham tDCS group.
Kurimori et al. (2015)	9	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right deltoid	2	–	20 min, 10 sessions (1 per weekday for 2 consecutive weeks)	PANSS	Improvement in negative but not positive symptoms post-tDCS.	No mention of DSM/ICD diagnosis.
Mondino et al. (2015b)	28	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Left TPJ	2	35	20 min, 10 sessions (2 per day for 5 consecutive days)	AVH frequency	Reduction in AVH after active versus sham tDCS.	No mention of DSM/ICD diagnosis. 15 participants were from Brunelin et al. (2012a). AVH frequency method of assessment not stated.
Praharaj et al. (2015)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	25	20 min, 5 sessions (1 per day for 5 consecutive days)	PSYRATS (AHS)	Reduction in AH post-tDCS, but symptoms returned to baseline levels 6 days after treatment.	No mention of DSM/ICD diagnosis.
Shenoy et al. (2015)	1	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	–	20 min, 10 sessions (2 per day for 5 consecutive days)	AHRS	Reduction in AVH post-tDCS, with further improvement for at least 1 month.	Participant was pregnant, and received tDCS treatment previously (reference given to conference abstract only).
Shivakumar et al. (2015)	23	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Left TPJ	2	35	20 min, 10 sessions (2 per	PSYRATS (AHS)	Reduction in AH post-tDCS.	Allelic variations in the COMT gene

Table 3 (*continued*)

Study	N[a]	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
		Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
								day for 5 consecutive days)			influenced the clinical efficacy of tDCS.
Smith et al. (2015)	29	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supraorbital area	2	5.08	20 min, 5 sessions (1 per day for 5 consecutive days in most cases)	PANSS, PSYRATS	No improvement in schizophrenic symptoms after active versus sham tDCS.	

AH, auditory hallucinations; AHRS, Auditory Hallucination Rating Scale; AHS, Auditory Hallucinations Subscale; AVH, auditory verbal hallucinations; BFCRS, Bush-Francis Catatonia Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; COMT, Catechol-O-methyltransferase; DLPFC, dorsolateral prefrontal cortex; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECT, electroconvulsive therapy; HCS, Hallucination Change Scale; ICD, International Classification of Diseases; LHS, Launay Slade Hallucination Scale; PANSS, Positive And Negative Syndrome Scale; PSYRATS, Psychotic Symptom Rating Scales; SANS, Scale for the Assessment of Negative Symptoms; tDCS, transcranial direct current stimulation; TPJ, temporo-parietal junction; VH, visual hallucinations.

[a] *N* refers to the number of participants whose data was included at the final stage of analysis.

tDCS/placebo pill (tDCS-only), or active tDCS/sertraline (combined treatment) (the tDCS intervention consisted of 10 consecutive weekday sessions followed by 2 extra sessions every other week) (Brunoni et al., 2013b). On the basis of MADRS scores, tDCS-only was more effective than placebo, but the combined treatment was superior to all other groups (Brunoni et al., 2013b). In phase II of the trial, willing non-responders who received sham tDCS in phase I ($n = 23$) underwent 10 sessions of active tDCS and moderate improvements in depressive symptomology were observed (Valiengo et al., 2013). During phase III, active tDCS responders from phase I and II ($n = 42$) received 24 weeks of maintenance treatment and continued to respond for an average of 11.7 weeks (Valiengo et al., 2013).

Less promising results were obtained by Blumberger et al. (2012), who found that 15 sessions of sham-controlled bilateral DLPFC tDCS did not lower HRSD scores in 24 patients with treatment-resistant MDD. Additionally, Shiozawa et al. (2015) described a patient – with inferred right hemispheric dominance – whose depressive symptoms intensified (according to HRSD scores) following five sessions of anodal left/cathodal right DLPFC tDCS. Brunoni et al. (2014a) showed that in 37 MDD patients, active tDCS (10 sessions) combined with cognitive control therapy (CCT) was not superior to sham tDCS combined with CCT. This is in contrast to a study by Segrave et al. (2014), in which concurrent CCT potentiated antidepressant outcomes (MADRS, BDI) from anodal l-DLPFC tDCS (the cathode was placed over the right lateral orbit). D'Urso et al. (2013) also described the effects of adjunctive tDCS and cognitive therapy: in a patient with refractory MDD, the therapeutic response to 10 sessions of bilateral DLPFC tDCS (indexed by the HRSD) was substantially more enduring when the treatment was coupled with weekly cognitive behavioural therapy (CBT).

To date, two studies using tDCS to treat major depression have targeted an alternative site to the DLPFC. In these open-label trials, improvements in symptoms (indexed by the MADRS) were observed following modulation of the fronto-occipital (Ho et al., 2014) or -temporal regions (Ho et al., 2015) (20 sessions) in a total of 18 patients with MDD.

3.3.2. Schizophrenia

Studies examining the clinical effects of tDCS in schizophrenia have mostly employed an electrode montage in which the anode is placed over the l-DLPFC and the cathode is positioned over the left temporoparietal junction (l-TPJ). This set-up appears to have been consistently successful in ameliorating symptoms of the illness; for example, Brunelin et al. (2012a) demonstrated that in 30 patients, 10 sessions of twice-daily sham-controlled tDCS robustly reduced auditory verbal hallucinations (AVHs; indexed by the Auditory Hallucination Rating Scale [AHRS]) acutely and at 3-month follow-up. Improvements in other schizophrenic symptoms, according to the total Positive and Negative Syndrome Scale (PANSS) score, were also recorded (Brunelin et al., 2012a). Mondino et al. (2015b) administered the same treatment protocol to a group of 28 patients, 15 of whom had previously taken part in the aforementioned study (Brunelin et al., 2012a), and also observed a large decrease in treatment-resistant AVH frequency in the active versus sham tDCS group.

Additional evidence of efficacy for this tDCS montage and protocol (10 twice-daily sessions, anode l-DLPFC/cathode l-TPJ) comes from three further open-label trials in which a total of 60 schizophrenic patients with persistent auditory hallucinations (AHs) presented significant reductions in Psychotic Symptoms Rating Scales (PSYRATS)/AHRS scores following treatment (Bose et al., 2014; Brunelin et al., 2015; Shivakumar et al., 2015). While all participants experienced improvements, being a non-smoker (Brunelin et al., 2015) and carrying a particular variant of a neuroplasticity-related gene (catechol-O-methyltransferase [COMT]) (Shivakumar et al., 2015) were both associated with having a greater therapeutic response. A number of case reports/series describing patients with refractory schizophrenia have also offered support (Brunelin et al., 2012b; Jacks et al., 2014; Narayanaswamy et al., 2014; Nawani et al., 2014a, 2014b; Rakesh et al., 2013; Shenoy et al., 2015; Shivakumar et al., 2014). For instance, Shenoy et al. (2015) recorded near-total improvement of the exacerbation of AVHs during pregnancy, Narayanaswamy et al. (2014) noted a delayed but persistent improvement in negative symptoms, and Rakesh et al. (2013) observed complete cessation of AVHs immediately after the first two tDCS sessions and at post-intervention reassessment. Shivakumar et al. (2014) also witnessed a tDCS-induced termination of AVHs, and subsequently found that application of intermittent booster tDCS (6 sessions) resulted in sustained improvements for a period of one year.

Less positive results were obtained in one case report of a patient presenting with severe, treatment-resistant symptoms who received a higher acute dose of tDCS (20 twice-daily sessions, anode l-DLPFC/cathode l-TPJ) but did not show any clinical gains (Shiozawa et al., 2014c). In addition, although Praharaj et al. (2015) did observe a reduction of AHs in a patient with treatment-resistant schizophrenia following 10 sessions of tDCS, PSYRATS scores returned to baseline levels six days later. Interestingly, Bose et al. (2015) documented a lack of clinical response to 18 twice-daily sessions of anode l-DLPFC/cathode l-TPJ tDCS in a patient with treatment resistant AVHs; however, significant improvements in

Table 4
Studies in patients with substance use disorders.

Study	N[a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
Boggio et al. (2008b)	13	Alcohol dependence	Randomised, double-blind, sham-controlled, crossover	(i) anode left/ cathode right tDCS; (ii) anode right/ cathode left tDCS; (iii) sham tDCS	(i) Left DLPFC, (ii) Right DLPFC	(i) Right DLPFC, (ii) Left DLPFC	2	35	20 min, 1 session	AUQ	Reduction in alcohol craving after anode left/ cathode right tDCS and anode right/cathode left tDCS versus sham tDCS. Alcohol craving could not be increased by alcohol cues after active versus sham tDCS.	
Nakamura-Palacios et al. (2012)	49	Alcohol dependence	Randomised, single-blind, sham-controlled, crossover	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supradeltoid area	1	35	10 min, 1 session	OCDS	No reduction in alcohol craving after active versus sham tDCS.	Alcohol craving was not provoked with cues.
da Silva et al. (2013)	13	Alcohol dependence	Randomised, single-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Left DLPFC	Right supradeltoid area	2	35	20 min, 5 sessions (1 per week for 5 consecutive weeks)	OCDS, verbally assessed relapse rates	Reduction in alcohol craving after active versus sham tDCS, but trend for relapse during treatment in active tDCS group.	
Klauss et al. (2014)	33	Alcohol dependence	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Right DLPFC	Left DLPFC	2	35	13 min, 10 sessions (2 per day, with a 20 min interval, for 5 consecutive days)	Verbally assessed relapse rates, OCDS	No reduction in alcohol craving after active versus sham tDCS, but patients in the active tDCS group were more likely to survive for at least 6 months without relapse.	Alcohol craving was not provoked with cues.
Shahbabaie et al. (2014)	30	mAMP dependence	Randomised, double-blind, sham-controlled, crossover	(i) tDCS; (ii) sham tDCS	Right DLPFC	Left supraorbital area	2	35	20 min, 1 session	Self-reported mAMP craving (VAS), CICT	Reduction in mAMP craving at rest, but increase in cue-induced craving, during active versus sham tDCS.	Effects of tDCS were state-dependent.
Conti et al. (2014)	13	Crack-cocaine dependence	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Right DLPFC	Left DLPFC	2	35	20 min, 5 sessions (1 per day for 5 alternate days)	Relapses/ periods of abstinence	No between-group differences in relapse rates during the treatment period. At 3-month follow-up, more participants in the real than in the sham tDCS group maintained abstinence from crack-cocaine.	Only 50% of participants in the sham group completed all treatment sessions (compared to 86% in the real group).
Batista et al. (2015)	36	Crack-cocaine dependence	Randomised, double-blind, sham-controlled, parallel	(i) tDCS; (ii) sham tDCS	Right DLPFC	Left DLPFC	2	35	20 min, 5 sessions (1 per day for 5 alternate days)	Crack-cocaine craving (scale composed of 5 items from the OCDS)	Reduction in crack-cocaine craving after active versus sham tDCS, maintained for at least 1 week.	

AUQ, Alcohol Urge Questionnaire; CICT, Computerised Cue-Induced Craving Assessment Task; DLPFC, dorsolateral prefrontal cortex; mAMP, methamphetamine; OCDS, Obsessive Compulsive Drinking Scale; tDCS, transcranial direct current stimulation; VAS, visual analogue scale.
[a] *N* refers to the number of participants whose data was included at the final stage of analysis.

symptoms (indexed by the PSYRATS) were subsequently recorded after an additional 20 sessions in which the electrodes were placed at homologous sites on the right side of the brain.

Shiozawa et al. (2013b) conducted a case study of tDCS in patients with long-term, refractory schizophrenia, opting for a unique protocol targeted at the selective improvement of visual hallucinations (VHs) and AHs. Twenty sessions of tDCS were performed in two blocks with a 5-day interval between: for the first 10 sessions, the cathode was placed over the occipital area (to hypothetically inhibit VHs) and for the remaining 10 sessions over the l-TPJ (to hypothetically inhibit AHs) (Shiozawa et al., 2013b). The anode was positioned over the l-DLPFC throughout (Shiozawa et al., 2013b). Although a transitory increase in hallucinations was observed during the period of stimulation, this was followed by a reduction in VHs and AHs (assessed with the Launay Slade Hallucination Scale [LSHS] and the AHRS, respectively), as well as marked improvements in other positive, negative, and general symptoms (indexed by the PANSS) (Shiozawa et al., 2013b).

Table 5
Studies of patients with other psychiatric disorders (obsessive compulsive disorder, generalised anxiety disorder, and anorexia nervosa).

Study	N[a]	Diagnosis	Design		Stimulation protocol for experimental condition(s)					Outcomes extracted for this review	Findings	Comments
			Study type	Groups/ conditions	Anode electrode position	Cathode electrode position	Current strength (mA)	Electrode size (cm^2)	Duration, number, and frequency			
Volpato et al. (2013)	1	OCD (comorbid MDD and GAD)	Double-blind, sham-controlled	(i) tDCS; (ii) sham tDCS; (iii) rTMS; (iv) sham rTMS	Posterior neck base	Left DLPFC	2	35	20 min, 10 sessions (1 per weekday for 2 consecutive weeks)	Y-BOCS, HRSD, HRSA	No improvement in OCD symptoms, but improvement in depression and anxiety, after real versus sham tDCS.	
Shiozawa et al. (2014b)	1	GAD	Open-label, uncontrolled	(i) tDCS	Left deltoid	Right DLPFC	2	25	30 min, 15 sessions (1 per weekday for 3 consecutive weeks)	GAD-7, BAI, HRSA	Improvement in anxiety symptoms during tDCS treatment course. Patient was asymptomatic post-tDCS and at 1-month follow-up.	No mention of DSM/ICD diagnosis.
Khedr et al. (2014)	7	AN	Open-label, uncontrolled	(i) tDCS	Left DLPFC	Right arm	2	24 (100 for extracephalic electrode)	25 min, 10 sessions (1 per weekday for 2 consecutive weeks)	EAT, EDI	Improvement in eating disorder symptoms post-tDCS, maintained for at least 1 month. Large variability in responses.	
D'Urso et al. (2015)	1	OCD	Open-label, uncontrolled	(i) anodal tDCS; (ii) cathodal tDCS	(i) pre-SMA; (ii) right deltoid	(i) Right deltoid; (ii) pre-SMA	2	25	20 min, 20 sessions (1 per weekday for 4 consecutive weeks)	Y-BOCS	Worsening and improvement of OCD symptoms after anodal and cathodal tDCS, respectively. Overall reduction in symptoms at the end of treatment, maintained for at least 3 months.	The polarity of the electrodes was inverted after 10 sessions due to exacerbation of symptoms.
Mondino et al. (2015a)	1	OCD	Open-label, uncontrolled	(i) tDCS	Right occipital cortex	Left OFC	2	35 (100 for anode)	20 min, 10 sessions (2 per day for 5 consecutive days)	Y-BOCS	Delayed improvement in OCD symptoms, maintained for at least 1 month.	
Narayanaswamy et al. (2015)	2	OCD	Open-label, uncontrolled	(i) tDCS	Left pre-SMA/ SMA	Right supraorbital area	2	35	20 min, 20 sessions (2 per day for 10 consecutive days)	Y-BOCS	Improvement in OCD symptoms post-tDCS, maintained for at least 1 month/2 months.	

AN, anorexia nervosa; BAI, Beck Anxiety Inventory; DLPFC, dorsolateral prefrontal cortex; DSM, Diagnostic and Statistical Manual of Mental Disorders; EAT, Eating Attitudes Test; EDI, Eating Disorder Inventory; GAD, generalised anxiety disorder; GAD-7, Generalised Anxiety Disorder 7-item scale; HRSA, Hamilton Rating Scale for Anxiety; HRSD, Hamilton Rating Scale for Depression; ICD, International Classification of Diseases; MDD, major depressive disorder; OCD, obsessive compulsive disorder; OFC, orbitofrontal cortex; rTMS, repetitive transcranial magnetic stimulation; SMA, supplementary motor area; tDCS, transcranial direct current stimulation; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

[a] *N* refers to the number of participants whose data was included at the final stage of analysis.

A number of other electrode montages have also been trialled for the treatment of schizophrenia, and findings have been mixed. For example, Palm et al. (2013) observed considerable improvement in positive and negative symptoms (using several clinical assessment tools) following a 2-week course of anodal tDCS to the l-DLPFC (the cathode was placed over the right supraorbital area) in a patient with refractory schizophrenia. In contrast, 29 patients who received 5 sessions of sham-controlled tDCS at the same parameters experienced no clinical benefits (indexed by the PANSS and the PSYRATS) (Smith et al., 2015). Shiozawa et al. (2013a) described a treatment-resistant patient who achieved complete remission from catatonic symptoms (indexed by the Bush–Francis catatonic scale) in response to 10 sessions of tDCS over the bilateral DLPFC (anodal left/cathodal right). Gomes et al. (2015) later replicated this protocol in an RCT of 15 participants and correspondingly found a reduction in negative symptoms (according to the PANSS) after active versus sham tDCS. Although no effects were reported for positive symptoms, the real tDCS group had higher scores on the positive subscale of the PANSS at baseline. An improvement in negative but not positive symptoms was also demonstrated by 9 further patients following 10 sessions of anodal l-DLPFC tDCS (with the cathode placed extracephalically) (Kurimori et al., 2015). Finally, Homan et al. (2011) showed that 10 sessions of cathodal stimulation over Wernicke's area (the anode was positioned over the right supraorbital area) led to persisting reductions in AVHs and other symptoms (indexed by the Hallucination Change Scale, PANSS, and the PSYRATS) in a patient with treatment-resistant schizophrenia.

3.3.3. Substance use disorders

The literature on the clinical utility of tDCS for treating SUDs consists of a small number of RCTs which have generated mixed results. Boggio et al. (2008b) were the first to publish data here: in a group of 13 participants with alcohol dependence, one session of tDCS to the bilateral DLPFC (either anodal left/cathodal right or anodal right/cathodal left) was shown to decrease alcohol craving (indexed by the Alcohol Urge Questionnaire [AUQ]) relative to sham stimulation. Interestingly, Klauss et al. (2014) found that a higher dose of bilateral DLPFC tDCS (10 twice-daily sessions) did not diminish craving (assessed with the Obsessive Compulsive Drinking Scale [OCDS]) but reduced relapse probability in 33 alcohol dependent individuals (Klauss et al., 2014). A dissociation between levels of craving and the likelihood of relapse to alcohol use was also reported by da Silva et al. (2013): 13 alcoholics received 5 weekly sessions of sham-controlled unilateral DLPFC stimulation (anode over the l-DLPFC, cathode over the right supradeltoid area) and, although the treatment suppressed cravings (indexed by the OCDS), there was an unexpected trend for more relapses in the active versus sham tDCS group. The same electrode montage was adopted in a single-session trial involving 49 alcohol-dependent patients in which no anti-craving effects were observed (Nakamura-Palacios et al., 2012).

Three studies examining the therapeutic potential of tDCS in individuals addicted to substances other than alcohol have been conducted. In the first, Shahbabaie et al. (2014) provided evidence suggesting that tDCS has a state-dependent effect on craving in methamphetamine (mAMP) users. Thirty patients underwent one session of sham-controlled anodal tDCS over the right DLPFC (r-DLPFC) (the cathode was placed over the left supraorbital area) and, while active tDCS acutely reduced craving at rest, it increased craving during mAMP-related cue exposure. In the second, Conti et al. (2014) administered 5 sessions of real or sham bilateral DLPFC stimulation (anodal right/cathode left) to 13 crack-cocaine addicted individuals and observed a higher percentage of abstinence at 3-month follow-up in those assigned to the real tDCS group. This study was later replicated using a larger group of patients ($n = 36$), whose crack-cocaine cravings were suppressed for at least one week by active versus sham tDCS (Batista et al., 2015).

3.3.4. Other psychiatric disorders

Limited data exist on the clinical efficacy of tDCS in other psychiatric disorders; however, some promising results have been reported. For example, Shiozawa et al. (2014b) described the case of a patient with treatment-resistant GAD who underwent a three-week course of cathodal r-DLPFC tDCS (the anode was placed over the left deltoid) and was asymptomatic both acutely and at one-month follow-up. Additionally, Khedr et al. (2014) showed that 10 sessions of anodal stimulation over the l-DLPFC (the cathode was positioned over the right arm) relieved eating disorder symptoms in 5 of 7 AN patients and, furthermore, 4 participants maintained these improvements for at least 1 month after the end of treatment.

Mondino et al. (2015a) demonstrated that 10 sessions of twice-daily cathodal tDCS over the left OFC (the anode was positioned over the right occipital cortex) induced delayed but lasting reductions in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores in a patient with treatment-resistant OCD. Sustained symptom improvements were also recorded in two patients with drug-resistant OCD, following 20 sessions of twice-daily anodal tDCS over the left pre-SMA/SMA (the cathode was placed over the right supraorbital area) (Narayanaswamy et al., 2015). Interestingly, D'Urso et al. (2015) found that a two-week course of anodal tDCS over the same region (with the cathode placed extracephalically) exacerbated a patient's OCD symptoms. The electrodes were then inverted for a further 10 sessions, which reduced Y-BOC scores (beyond baseline levels) for at least 3 months post-treatment (D'Urso et al., 2015). Lastly, Volpato et al. (2013) administered 10 sessions of cathodal l-DLPFC tDCS (with the anode placed over the posterior neck base) to a patient with severe and enduring OCD and, although the intervention had no effect on OCD-specific symptoms (indexed by the Y-BOCS), it improved the patient's comorbid anxiety and depression (assessed with the Hamilton Rating Scale for Anxiety [HRSA] and the HRSD, respectively).

4. Discussion

4.1. Clinical efficacy

This review provides evidence that tDCS has the potential to ameliorate symptoms associated with several major psychiatric disorders. Most notably, data from a number of RCTs suggest that tDCS interventions comprised of multiple sessions can induce enduring therapeutic effects in patients with depressive disorders and schizophrenia. Further indication of clinical utility in these conditions has come from numerous open-label trials and case reports, often involving patients who have experienced dramatic improvements and, in some instances, achieved full remission following treatment with tDCS. Although research in other mental disorders is somewhat limited, several RCTs support the prospective application of tDCS in SUDs, and emerging data from a small number of patients indicate that tDCS can induce significant clinical gains in people with OCD, GAD, and AN.

Despite evidence that tDCS offers exciting possibilities for treatment development in psychiatry, symptom improvements have been modest or absent in a considerable number of studies. Furthermore, a small number of publications have reported a tDCS-induced exacerbation of symptoms. Multiple factors are likely to contribute to the variability of response in tDCS studies, and these are discussed in turn below.

4.2. Patient characteristics

A number of interindividual biological, psychological, and lifestyle factors appear to influence the clinical efficacy of tDCS. First, differences in genotype have been linked to altered tDCS responding, possibly via impact on anatomical and neurophysiological states. Shivakumar et al. (2015), for example, showed that a polymorphism at the neuroplasticity-related COMT gene moderated the therapeutic effects of tDCS in a group of patients with schizophrenia. Second, the psychological state of participants at the time of stimulation seems to play a role: in SUD, prefrontal tDCS has been found to intensify cravings if those receiving it are in the presence of drug-related cues (Shahbabaie et al., 2014). Third, nicotine smoking has been associated with reduced clinically efficacy of tDCS in patients with schizophrenia (Brunelin et al., 2015). This may explain the negative results reported by Smith et al. (2015), since all participants in this study were regular smokers. Fourth, illness severity has been identified as a predictor of response to tDCS: Ferrucci et al. (2009a) observed a greater therapeutic effect for severe MDD than for mild/moderate MDD.

It has been proposed that degree of treatment-resistance may also influence clinical outcomes of tDCS (Brunoni and Fregni, 2011; Mondino et al., 2014), although this factor has not been explicitly investigated and studies of patients with treatment-resistant disorders have produced both negative (e.g., Bennabi et al., 2015; Blumberger et al., 2012; Palm et al., 2012) and positive (e.g., Dell'Osso et al., 2012; Ferrucci et al., 2009b; Palm et al., 2013) results. Nevertheless, close attention must be paid to the definition of treatment-resistance because, in some instances, studies with negative results (Blumberger et al., 2012; Palm et al., 2012) have used more stringent refractoriness criteria than those with positive ones (Dell'Osso et al., 2012).

4.3. Concomitant therapy

The medication status of patients varied significantly both within and between studies included in this review. In some cases, tDCS was administered as an "add-on" therapy to a stable dose of medication (e.g., Bose et al., 2014), while other studies excluded participants taking any neuropsychotropic drugs (e.g., Boggio et al., 2008b), included a mix of medicated and non-medicated patients (e.g., Loo et al., 2010), or failed to address concomitant pharmacotherapy at all (e.g., da Silva et al., 2013). Evidence indicates that particular psychoactive substances can interact with the effects of tDCS; specifically, benzodiazepines have been reported to hinder therapeutic effects, whereas antidepressants have been associated with enhanced outcomes (Brunoni et al., 2013a, 2013b). Crucially, three studies which found tDCS to be clinically ineffective permitted benzodiazepine use during the trial (26–33% of patients were taking benzodiazepines) (Bennabi et al., 2015; Blumberger et al., 2012; Brunoni et al., 2014a), and one study which found tDCS to be effective tolerated antidepressant but not benzodiazepine use (52% of patients were taking antidepressants) (Segrave et al., 2014). Nonetheless, Boggio et al. (2008a) used opposing eligibility criteria – allowing benzodiazepine but not antidepressant use – and still observed positive effects. Cognitive-based therapies can also influence clinical outcomes from tDCS (D'Urso et al., 2013; Segrave et al., 2014); however, information regarding the use of concurrent non-pharmacological treatments was seldom provided.

4.4. Parameters of stimulation

tDCS interventions varied extensively between the reviewed studies according to a range of parameters, such as electrode size and positioning, current amplitude, duration of stimulation, and number and frequency of sessions (see Tables 2–5). Considerable heterogeneity was even present among studies attempting to treat the same psychiatric disorder. Unsurprisingly, results from several investigations suggested that the number of sessions administered, the placement of the reference electrode, and the anode/cathode polarity moderate the therapeutic effects of tDCS (Bose et al., 2015; D'Urso et al., 2015; Loo et al., 2012, 2010; Martin et al., 2011). Most notably, D'Urso et al. (2015) demonstrated that 10 sessions of anodal tDCS applied to the pre-SMA led to an exacerbation of symptoms in a patient with OCD; however, when the polarity of the electrodes was inverted (for a further 10 sessions of tDCS), significant and persisting improvements beyond baseline levels were observed.

4.5. Study design

This review incorporated studies of varying design. Interestingly, the majority of studies with negative results were RCTs (e.g., Blumberger et al., 2012; Klauss et al., 2014; Loo et al., 2012; Nakamura-Palacios et al., 2012; Palm et al., 2012; Smith et al., 2015), which raises the possibility of a placebo effect. Indeed, sham tDCS frequently exerts some degree of influence over outcomes; however, the improvements observed in open-label investigations are unlikely to be the result of placebo mechanisms alone since many of the patients involved in these studies were treatment-resistant, and refractoriness is associated with lower placebo responding (Brunoni et al., 2009). It should also be noted that publication bias – in which research with unfavourable results has a lower probability of being published – is more likely to affect open-label, uncontrolled studies than RCTs (Easterbrook et al., 1991). Thus, the higher proportion of RCTs with negative results may be, at least in part, an artefact of such bias.

4.6. Safety issues and ethical considerations

Administration of tDCS interventions that comply with recommended safety regulations (current: <2.5 mA, duration: 20–60 min per session, frequency: ≤ twice per day, application: with electrodes that minimise skin burns) (Fregni et al., 2015) has presented minimal risk across a wide range of participants. Only mild and transient side-effects – such as itching, tingling, and headache – have been reported (Brunoni et al., 2011a), leading to the conclusion that tDCS is a relatively safe procedure. However, the absence of serious adverse events is not irrefutable evidence that the technique is unequivocally benign, and a number of ethical and safety issues remain (Fitz and Reiner, 2015; Kadosh et al., 2012; Widdows and Davis, 2014).

Firstly, Brunoni et al. (2011a) argue that adverse events are being neglected in tDCS research, possibly due to a subjective belief that the technique raises negligible safety concerns. In their systematic review of 209 tDCS clinical trials, 92 studies did not report the presence and/or absence of adverse effects, which the authors interpret as evidence of selective reporting bias (Brunoni and Fregni, 2011). Secondly, despite knowledge that stimulation of one particular cortical site can alter activation and connectivity in regions distal to the electrodes, the nature of the functional networks associated with the target brain areas seems to have little influence in the design of tDCS experiments (Wokke et al., 2014). Data suggest that cognitive enhancement mediated by tDCS can occur at the expense of other cognitive functions (Iuculano and Cohen Kadosh, 2013), yet the potential for collateral behavioural impairments arising from the use of tDCS in psychiatric research has been largely overlooked. Our incomplete

understanding of the neural bases of mental disorders and the resultant lack of any standardised stimulation guidelines pose risks for the occurrence of unintended and undesirable effects. Thirdly, Widdows and Davis (2014) point out that qualitative differences in anatomy are sometimes seen in people with mental illness compared to healthy controls; for example, patients with eating disorders have shown low levels of subcutaneous adipose tissue around the head and altered cortical folding. These factors are likely to have an impact on the effects of tDCS-induced electrical currents, therefore extra caution ought to be exercised in such patient groups (Widdows and Davis, 2014). Lastly, tDCS has recently garnered considerable 'neuro-hype' in the media as a portable, painless, inexpensive, and safe therapeutic device. This positive portrayal has the potential to shape the public's risk-benefit perceptions, promote a therapeutic misconception, and have an impact on the uptake of this technology (Dubljević et al., 2014). Without some degree of 'neuromodesty' (Morse, 2012), desperate and vulnerable mentally ill patients may overestimate the benefits and underestimate the risks of tDCS.

5. Conclusions and future directions

Research into the clinical efficacy of tDCS in psychiatric disorders has grown exponentially over the past decade. We have systematically reviewed the literature and have provided an objective and analytical account of its current state. Overall, data from studies appraised in this review suggest that tDCS has the potential to induce clinically relevant behavioural changes in often difficult-to-treat patient populations, and could thus represent a valuable tool for intervention in a range of mental disorders. Nevertheless, the use of tDCS for treating psychiatric disorders is still in its infancy, and further evidence of its efficacy from large-scale, multi-centred RCTs is required if the transition of this therapy from the laboratory to the clinic is to be considered. Indeed, the approval of repetitive transcranial magnetic stimulation (a related non-invasive neuromodulation technique) as a second-line treatment for major depression in several countries was preceded by extensive sham-controlled investigations (Dell'Osso and Altamura, 2014). It is also essential that steps are taken to resolve the discrepancies in clinical findings; for example, sample variability should be controlled and reproducible stimulation parameters should be defined in terms of optimising therapeutic response for different clinical applications. A better understanding of the neural responses to tDCS will accelerate progress here, and is likely to arise through combined tDCS-neuroimaging experiments (Venkatakrishnan and Sandrini, 2012) and computational neurostimulation approaches (de Berker et al., 2013). Finally, all investigators conducting research with tDCS should be mindful of the various safety and ethical issues associated with the use of this neuromodulation technique.

Contributors

The authors were the only individuals who contributed to this publication.

Role of the funding source

This paper represents independent research part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. Maria Kekic is supported by an Institute of Psychiatry, Psychology and Neuroscience/Medical Research Council Excellence Studentship.

Acknowledgements

None to declare.

References

Alonso, J., Angermeyer, M.C., Bernert, S., Bruffaerts, R., Brugha, T.S., Bryson, H., et al., 2004. Disability and quality of life impact of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr. Scand. Suppl. 38–46.

Alonzo, A., Chan, G., Martin, D., Mitchell, P.B., Loo, C., 2013. Transcranial direct current stimulation (tDCS) for depression: analysis of response using a three-factor structure of the Montgomery-Asberg depression rating scale. J. Affect. Disord. 150, 91–95.

Batista, E.K., Klauss, J., Fregni, F., Nitsche, M.A., Nakamura-Palacios, E.M., 2015. A randomized placebo-controlled trial of targeted prefrontal cortex modulation with bilateral tDCS in patients with crack-cocaine dependence. Int. J. Neuropsychopharmacol. 18.

Bennabi, D., Nicolier, M., Monnin, J., Tio, G., Pazart, L., Vandel, P., et al., 2015. Pilot study of feasibility of the effect of treatment with tDCS in patients suffering from treatment-resistant depression treated with escitalopram. Clin. Neurophysiol. 126, 1185–1189.

Berlim, M.T., Van den Eynde, F., Daskalakis, Z.J., 2013. Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. J. Psychiatr. Res. 47, 1–7.

Blumberger, D.M., Tran, L.C., Fitzgerald, P.B., Hoy, K.E., Daskalakis, Z.J., 2012. A randomized double-blind sham-controlled study of transcranial direct current stimulation for treatment-resistant major depression. Front. Psychiatry 3, 74.

Boggio, P.S., Rigonatti, S.P., Ribeiro, R.B., Myczkowski, M.L., Nitsche, M.A., Pascual-Leone, A., et al., 2008a. A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. Int. J. Neuropsychopharmacol. 11, 249–254.

Boggio, P.S., Sultani, N., Fecteau, S., Merabet, L., Mecca, T., Pascual-Leone, A., et al., 2008b. Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: a double-blind, sham-controlled study. Drug Alcohol Depend. 92, 55–60.

Bose, A., Shivakumar, V., Narayanaswamy, J.C., Nawani, H., Subramaniam, A., Agarwal, S.M., et al., 2014. Insight facilitation with add-on tDCS in schizophrenia. Schizophr. Res. 156, 63–65.

Bose, A., Sowmya, S., Shenoy, S., Agarwal, S.M., Chhabra, H., Narayanaswamy, J.C., et al., 2015. Clinical utility of attentional salience in treatment of auditory verbal hallucinations in schizophrenia using transcranial direct current stimulation (tDCS). Schizophr. Res. 164, 279–280.

Brunelin, J., Mondino, M., Gassab, L., Haesebaert, F., Gaha, L., Suaud-Chagny, M.F., et al., 2012a. Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. Am. J. Psychiatry 169, 719–724.

Brunelin, J., Mondino, M., Haesebaert, F., Saoud, M., Suaud-Chagny, M.F., Poulet, E., 2012b. Efficacy and safety of bifocal tDCS as an interventional treatment for refractory schizophrenia. Brain Stimul. 5, 431–432.

Brunelin, J., Hasan, A., Haesebaert, F., Nitsche, M.A., Poulet, E., 2015. Nicotine smoking prevents the effects of frontotemporal transcranial Direct Current Stimulation (tDCS) in hallucinating patients with Schizophrenia. Brain Stimul. 8, 1225–1227.

Brunoni, A.R., Fregni, F., 2011. Clinical trial design in non-invasive brain stimulation psychiatric research. Int. J. Methods Psychiatr. Res. 20, e19–e30.

Brunoni, A.R., Lopes, M., Kaptchuk, T.J., Fregni, F., 2009. Placebo response of non-pharmacological and pharmacological trials in major depression: a systematic review and meta-analysis. PLoS One 4, e4824.

Brunoni, A.R., Amadera, J., Berbel, B., Volz, M.S., Rizzerio, B.G., Fregni, F., 2011a. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychopharmacol.

Brunoni, A.R., Ferrucci, R., Bortolomasi, M., Vergari, M., Tadini, L., Boggio, P.S., et al., 2011b. Transcranial direct current stimulation (tDCS) in unipolar vs. bipolar depressive disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 35, 96–101.

Brunoni, A.R., Ferrucci, R., Fregni, F., Boggio, P.S., Priori, A., 2012a. Transcranial direct current stimulation for the treatment of major depressive disorder: a summary of preclinical, clinical and translational findings. Prog. Neuropsychopharmacol. Biol. Psychiatry 39, 9–16.

Brunoni, A.R., Nitsche, M.A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., et al., 2012b. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul. 5, 175–195.

Brunoni, A.R., Ferrucci, R., Bortolomasi, M., Scelzo, E., Boggio, P.S., Fregni, F., et al., 2013a. Interactions between transcranial direct current stimulation (tDCS) and pharmacological interventions in the major depressive episode: findings from a naturalistic study. Eur. Psychiatry 28, 356–361.

Brunoni, A.R., Valiengo, L., Baccaro, A., Zanao, T.A., de Oliveira, J.F., Goulart, A., et al., 2013b. The sertraline vs. electrical current therapy for treating depression

clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiatry 70, 383–391.
Brunoni, A.R., Boggio, P.S., De Raedt, R., Bensenor, I.M., Lotufo, P.A., Namur, V., et al., 2014a. Cognitive control therapy and transcranial direct current stimulation for depression: a randomized, double-blinded, controlled trial. J. Affect Disord. 162, 43–49.
Brunoni, A.R., Junior, R.F., Kemp, A.H., Lotufo, P.A., Bensenor, I.M., Fregni, F., 2014b. Differential improvement in depressive symptoms for tDCS alone and combined with pharmacotherapy: an exploratory analysis from the Sertraline vs. Electrical current therapy for treating depression clinical Study. Int. J. Neuropsychopharmacol. 17, 53–61.
Chan, H.N., Alonzo, A., Martin, D.M., Mitchell, P.B., Sachdev, P., Loo, C.K., 2013. Augmenting transcranial direct current stimulation with (D)-cycloserine for depression: a pilot study. J. ECT 29, 196–200.
Conti, C.L., Moscon, J.A., Fregni, F., Nitsche, M.A., Nakamura-Palacios, E.M., 2014. Cognitive Related Electrophysiological Changes Induced by Non-invasive Cortical Electrical Stimulation in Crack-cocaine Addiction.
D'Urso, G., Mantovani, A., Micillo, M., Priori, A., Muscettola, G., 2013. Transcranial direct current stimulation and cognitive-behavioral therapy: evidence of a synergistic effect in treatment-resistant depression. Brain Stimul. 6, 465–467.
D'Urso, G., Brunoni, A.R., Anastasia, A., Micillo, M., de Bartolomeis, A., Mantovani, A., 2015. Polarity-dependent effects of transcranial direct current stimulation in obsessive-compulsive disorder. Neurocase 22, 60–64.
da Silva, M.C., Conti, C.L., Klauss, J., Alves, L.G., do Nascimento Cavalcante, H.M., Fregni, F., et al., 2013. Behavioral effects of transcranial direct current stimulation (tDCS) induced dorsolateral prefrontal cortex plasticity in alcohol dependence. J. Physiol. Paris 107, 493–502.
de Berker, A.O., Bikson, M., Bestmann, S., 2013. Predicting the behavioral impact of transcranial direct current stimulation: issues and limitations. Front. Hum. Neurosci. 7, 613.
Dell'Osso, B., Zanoni, S., Ferrucci, R., Vergari, M., Castellano, F., D'Urso, N., et al., 2012. Transcranial direct current stimulation for the outpatient treatment of poor-responder depressed patients. Eur. Psychiatry 27, 513–517.
Dell'Osso, B., Dobrea, C., Arici, C., Benatti, B., Ferrucci, R., Vergari, M., et al., 2014. Augmentative transcranial direct current stimulation (tDCS) in poor responder depressed patients: a follow-up study. CNS Spectrums 19, 347–354.
Dell'Osso, B., Altamura, A.C., 2014. Transcranial brain stimulation techniques for major depression: should we extend TMS lessons to tDCS? clinical practice and epidemiology in mental health. CP EMH 10, 92–93.
Dubljević, V., Saigle, V., Racine, E., 2014. The rising tide of tDCS in the Media and academic literature. Neuron 82, 731–736.
Easterbrook, P.J., Gopalan, R., Berlin, J.A., Matthews, D.R., 1991. Originally published as Volume 1, Issue 8746Publication bias in clinical research. Lancet 337, 867–872.
Ferrucci, R., Bortolomasi, M., Brunoni, A.R., Vergari, M., Tadini, L., Giacopuzzi, M., et al., 2009a. Comparative benefits of transcranial direct current stimulation (tDCS) treatment in patients with mild/moderate vs. severe depression. Clin. Neuropsychiatry 6, 246–251.
Ferrucci, R., Bortolomasi, M., Vergari, M., Tadini, L., Salvoro, B., Giacopuzzi, M., et al., 2009b. Transcranial direct current stimulation in severe, drug-resistant major depression. J. Affect Disord. 118, 215–219.
Fitz, N.S., Reiner, P.B., 2015. The challenge of crafting policy for do-it-yourself brain stimulation. J. Med. Ethics 41, 410–412.
Frangou, S., 2014. A systems neuroscience perspective of schizophrenia and bipolar disorder. Schizophr. Bull. 40, 523–531.
Fregni, F., Boggio, P.S., Nitsche, M.A., Marcolin, M.A., Rigonatti, S.P., Pascual-Leone, A., 2006a. Treatment of major depression with transcranial direct current stimulation. Bipolar Disord. 8, 203–204.
Fregni, F., Boggio, P.S., Nitsche, M.A., Rigonatti, S.P., Pascual-Leone, A., 2006b. Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression. Depress Anxiety 23, 482–484.
Fregni, F., Nitsche, M.A., Loo, C.K., Brunoni, A.R., Marangolo, P., Leite, J., et al., 2015. Regulatory considerations for the clinical and research use of transcranial direct current stimulation (tDCS): review and recommendations from an expert panel. Clin. Res. Regul. Aff. 32, 22–35.
George, M.S., Aston-Jones, G., 2010. Noninvasive techniques for probing neurocircuitry and treating illness: vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Neuropsychopharmacology 35, 301–316.
Gomes, J.S., Shiozawa, P., Dias, A.M., Valverde Ducos, D., Akiba, H., Trevizol, A.P., et al., 2015. Left dorsolateral prefrontal cortex anodal tDCS effects on negative symptoms in Schizophrenia. Brain Stimul. 8, 989–991.
Ho, K.A., Bai, S., Martin, D., Alonzo, A., Dokos, S., Puras, P., et al., 2014. A pilot study of alternative transcranial direct current stimulation electrode montages for the treatment of major depression. J. Affect Disord. 167, 251–258.
Ho, K.A., Bai, S., Martin, D., Alonzo, A., Dokos, S., Loo, C.K., 2015. Clinical pilot study and computational modeling of bitemporal transcranial direct current stimulation, and safety of repeated courses of treatment, in major depression. J. ECT 31, 226–233.
Homan, P., Kindler, J., Federspiel, A., Flury, R., Hubl, D., Hauf, M., et al., 2011. Muting the voice: a case of arterial spin labeling-monitored transcranial direct current stimulation treatment of auditory verbal hallucinations. Am. J. Psychiatry 168, 853–854.
Insel, T.R., 2014. A New Approach to Clinical Trials.
Insel, T.R., Gogtay, N., 2014. National Institute of mental health clinical trials: new opportunities, new expectations. JAMA psychiatry 71, 745–746.
Iuculano, T., Cohen Kadosh, R., 2013. The mental cost of cognitive enhancement. J. Neurosci. 33, 4482–4486.
Jacks, S., Kalivas, B., Mittendorf, A., Kindt, C., Short, E.B., 2014. Transcranial direct-current stimulation as an adjunct to electroconvulsive therapy and clozapine for refractory psychosis. Prim. Care Companion CNS Disord. 16. PCC.14l01635.
Kadosh, R.C., Levy, N., O'Shea, J., Shea, N., Savulescu, J., 2012. The neuroethics of non-invasive brain stimulation. Curr. Biol. 22, R108–R111.
Kalu, U.G., Sexton, C.E., Loo, C.K., Ebmeier, K.P., 2012. Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. Psychol. Med. 42, 1791–1800.
Kessler, R.C., Demler, O., Frank, R.G., Olfson, M., Pincus, H.A., Walters, E.E., et al., 2005. Prevalence and treatment of mental disorders, 1990 to 2003. N. Engl. J. Med. 352, 2515–2523.
Khedr, E.M., Elfetoh, N.A., Ali, A.M., Noamany, M., 2014. Anodal transcranial direct current stimulation over the dorsolateral prefrontal cortex improves anorexia nervosa: a pilot study. Restor. Neurol. Neurosci. 32, 789–797.
Klauss, J., Penido Pinheiro, L.C., Silva Merlo, B.L., de Almeida Correia Santos, G., Fregni, F., Nitsche, M.A., et al., 2014. A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. Int. J. Neuropsychopharmacol. 17, 1793–1803.
Knotkova, H., Rosedale, M., Strauss, S.M., Horne, J., Soto, E., Cruciani, R.A., et al., 2012. Using transcranial direct current stimulation to treat depression in HIV-infected persons: the outcomes of a feasibility study. Front. Psychiatry 3, 59.
Kuo, M.F., Paulus, W., Nitsche, M.A., 2014. Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. Neuroimage 85 (Pt 3), 948–960.
Kurimori, M., Shiozawa, P., Bikson, M., Aboseria, M., Cordeiro, Q., 2015. Targeting negative symptoms in schizophrenia: results from a proof-of-concept trial assessing prefrontal anodic tDCS protocol. Schizophr. Res. 166, 362–363.
Loo, C.K., Sachdev, P., Martin, D., Pigot, M., Alonzo, A., Malhi, G.S., et al., 2010. A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression. Int. J. Neuropsychopharmacol. 13, 61–69.
Loo, C.K., Alonzo, A., Martin, D., Mitchell, P.B., Galvez, V., Sachdev, P., 2012. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. Br. J. Psychiatry 200, 52–59.
Martin, D.M., Alonzo, A., Mitchell, P.B., Sachdev, P., Galvez, V., Loo, C.K., 2011. Fronto-extracephalic transcranial direct current stimulation as a treatment for major depression: an open-label pilot study. J. Affect Disord. 134, 459–463.
Martin, D.M., Alonzo, A., Ho, K.A., Player, M., Mitchell, P.B., Sachdev, P., et al., 2013. Continuation transcranial direct current stimulation for the prevention of relapse in major depression. J. Affect Disord. 144, 274–278.
Medical Research Council, 2010. Review of Mental Health Research: Report of the Strategic Review Group, p. 2010.
Meron, D., Hedger, N., Garner, M., Baldwin, D.S., 2015. Transcranial direct current stimulation (tDCS) in the treatment of depression: systematic review and meta-analysis of efficacy and tolerability. Neurosci. Biobehav Rev. 57, 46–62.
Mondino, M., Bennabi, D., Poulet, E., Galvao, F., Brunelin, J., Haffen, E., 2014. Can transcranial direct current stimulation (tDCS) alleviate symptoms and improve cognition in psychiatric disorders? World J. Biol. Psychiatry 15, 261–275.
Mondino, M., Haesebaert, F., Poulet, E., Saoud, M., Brunelin, J., 2015a. Efficacy of cathodal transcranial direct current stimulation over the left orbitofrontal cortex in a patient with treatment-resistant obsessive-compulsive disorder. J. ECT 31, 271–272.
Mondino, M., Haesebaert, F., Poulet, E., Suaud-Chagny, M.F., Brunelin, J., 2015b. Fronto-temporal transcranial Direct Current Stimulation (tDCS) reduces source-monitoring deficits and auditory hallucinations in patients with schizophrenia. Schizophr. Res. 161, 515–516.
Mondino, M., Brunelin, J., Palm, U., Brunoni, A.R., Poulet, E., Fecteau, S., 2015c. Transcranial direct current stimulation for the treatment of refractory symptoms of schizophrenia. Current evidence and future directions. Curr. Pharm. Des. 21, 3373–3383.
Morse, S.J., 2012. New therapies, old problems, or, a plea for neuromodesty. AJOB Neurosci. 3, 60–64.
Murray, C.J.L., Vos, T., Lozano, R., Naghavi, M., Flaxman, A.D., Michaud, C., et al., 2012. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380, 2197–2223.
Nakamura-Palacios, E.M., de Almeida Benevides, M.C., da Penha Zago-Gomes, M., de Oliveira, R.W., de Vasconcellos, V.F., de Castro, L.N., et al., 2012. Auditory event-related potentials (P3) and cognitive changes induced by frontal direct current stimulation in alcoholics according to Lesch alcoholism typology. Int. J. Neuropsychopharmacol. 15, 601–616.
Narayanaswamy, J.C., Shivakumar, V., Bose, A., Agarwal, S.M., Venkatasubramanian, G., Gangadhar, B.N., 2014. Sustained improvement of negative symptoms in schizophrenia with add-on tDCS: a case report. Clin. Schizophr. Relat. Psychoses 8, 135–136.
Narayanaswamy, J.C., Jose, D., Chhabra, H., Agarwal, S.M., Shrinivasa, B., Hegde, A., et al., 2015. Successful application of add-on transcranial Direct Current Stimulation (tDCS) for treatment of SSRI resistant OCD. Brain Stimul. 8 (3), 655–657.
Nawani, H., Bose, A., Agarwal, S.M., Shivakumar, V., Chhabra, H., Subramaniam, A., et al., 2014a. Modulation of corollary discharge dysfunction in schizophrenia by tDCS: preliminary evidence. Brain Stimul. 7, 486–488.
Nawani, H., Kalmady, S.V., Bose, A., Shivakumar, V., Rakesh, G., Subramaniam, A., et al., 2014b. Neural basis of tDCS effects on auditory verbal hallucinations in

schizophrenia: a case report evidence for cortical neuroplasticity modulation. J. ECT 30, e2–4.
Palm, U., Keeser, D., Schiller, C., Fintescu, Z., Reisinger, E., Baghai, T.C., et al., 2009. Transcranial direct current stimulation in a patient with therapy-resistant major depression. World J. Biol. Psychiatry 10, 632–635.
Palm, U., Schiller, C., Fintescu, Z., Obermeier, M., Keeser, D., Reisinger, E., et al., 2012. Transcranial direct current stimulation in treatment resistant depression: a randomized double-blind, placebo-controlled study. Brain Stimul. 5, 242–251.
Palm, U., Keeser, D., Blautzik, J., Pogarell, O., Ertl-Wagner, B., Kupka, M.J., et al., 2013. Prefrontal transcranial direct current stimulation (tDCS) changes negative symptoms and functional connectivity MRI (fcMRI) in a single case of treatment-resistant schizophrenia. Schizophr. Res. 150, 583–585.
Player, M.J., Taylor, J.L., Weickert, C.S., Alonzo, A., Sachdev, P.S., Martin, D., et al., 2014. Increase in PAS-induced neuroplasticity after a treatment course of transcranial direct current stimulation for depression. J. Affect Disord. 167, 140–147.
Praharaj, S.K., Behere, R.V., Sharma, P.S., 2015. Cathodal transcranial direct current stimulation over left temporoparietal area for treatment-refractory delusions and auditory hallucinations in schizophrenia: a case study. J. ECT 31, 277–278.
Price, J.L., Drevets, W.C., 2013. Neural circuitry of depression. In: Charney, S., Sklar, P., Buxbaum, J.D., Nestler, E.J. (Eds.), Neurobiology of Mental Illness, fourth ed. Oxford University Press, New York, pp. 455–469.
Rakesh, G., Shivakumar, V., Subramaniam, A., Nawani, H., Amaresha, A.C., Narayanaswamy, J.C., et al., 2013. Monotherapy with tDCS for Schizophrenia: a case report. Brain Stimul. 6, 708–709.
Schmidt, L.M., Gotzsche, P.C., 2005. Of mites and men: reference bias in narrative review articles: a systematic review. J. Fam. Pract. 54, 334–338.
Segrave, R.A., Arnold, S., Hoy, K., Fitzgerald, P.B., 2014. Concurrent cognitive control training augments the antidepressant efficacy of tDCS: a pilot study. Brain Stimul. 7, 325–331.
Shahbabaie, A., Golesorkhi, M., Zamanian, B., Ebrahimpoor, M., Keshvari, F., Nejati, V., et al., 2014. State dependent effect of transcranial direct current stimulation (tDCS) on methamphetamine craving. Int. J. Neuropsychopharmacol. 17, 1591–1598.
Shenoy, S., Bose, A., Chhabra, H., Dinakaran, D., Agarwal, S.M., Shivakumar, V., et al., 2015. Transcranial Direct Current Stimulation (tDCS) for auditory verbal hallucinations in schizophrenia during pregnancy: a case report. Brain stimul.: Basic, Transl. Clin. Res. Neuromodulation 8, 163–164.
Shiozawa, P., da Silva, M.E., Cordeiro, Q., Fregni, F., Brunoni, A.R., 2013a. Transcranial direct current stimulation (tDCS) for catatonic schizophrenia: a case study. Schizophr. Res. 146, 374–375.
Shiozawa, P., da Silva, M.E., Cordeiro, Q., Fregni, F., Brunoni, A.R., 2013b. Transcranial direct current stimulation (tDCS) for the treatment of persistent visual and auditory hallucinations in schizophrenia: a case study. Brain Stimul. 6, 831–833.
Shiozawa, P., da Silva, M.E., Dias, D.R., Chaves, A.C., de Oliveira Diniz, B.S., Cordeiro, Q., 2014a. Transcranial direct current stimulation for depression in a 92-year-old patient: a case study. Psychogeriatrics Off. J. Jpn. Psychogeriatr. Soc. 14, 269–270.
Shiozawa, P., Leiva, A.P., Castro, C.D., da Silva, M.E., Cordeiro, Q., Fregni, F., et al., 2014b. Transcranial direct current stimulation for generalized anxiety disorder: a case study. Biol. Psychiatry 75, e17–e18.
Shiozawa, P., Santos, M.M., Piovesan, F.X., Pellegrinelli, A., Enokibara da Silva, M., Bocato, M.Q., et al., 2014c. Cerebral blood flow changes after transcranial direct current stimulation for a patient with schizophrenia: a case report. J. Neuropsychiatry Clin. Neurosci. 26, E03–E05.
Shiozawa, P., Fregni, F., Bensenor, I.M., Lotufo, P.A., Berlim, M.T., Daskalakis, J.Z., et al., 2014d. Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. Int. J. Neuropsychopharmacol. 17, 1443–1452.
Shiozawa, P., da Silva, M.E., Cordeiro, Q., 2015. Transcranial direct current stimulation for treating depression in a patient with right hemispheric dominance: a case study. J. ECT 31, 201–202.
Shivakumar, V., Narayanaswamy, J.C., Agarwal, S.M., Bose, A., Subramaniam, A., Venkatasubramanian, G., 2014. Targeted, intermittent booster tDCS: a novel add-on application for maintenance treatment in a schizophrenia patient with refractory auditory verbal hallucinations. Asian J. Psychiatr. 11, 79–80.
Shivakumar, V., Chhabra, H., Subbanna, M., Agarwal, S.M., Bose, A., Kalmady, S.V., et al., 2015. Effect of tDCS on auditory hallucinations in schizophrenia: Influence of catechol-O-methyltransferase (COMT) Val158Met polymorphism. Asian J. Psychiatr. 16, 75–77.
Smith, R.C., Boules, S., Mattiuz, S., Youssef, M., Tobe, R.H., Sershen, H., et al., 2015. Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: a randomized controlled study. Schizophr. Res. 168, 260–266.
Thomas, B.H., Ciliska, D., Dobbins, M., Micucci, S., 2004. A process for systematically reviewing the literature: providing the research evidence for public health nursing interventions. Worldviews Evid. Based Nurs. 1, 176–184.
Tortella, G., Casati, R., Aparicio, L.V.M., Mantovani, A., Senço, N., D'Urso, G., et al., 2015. Transcranial direct current stimulation in psychiatric disorders. World J. Psychiatry 5, 88–102.
Valiengo, L., Bensenor, I.M., Goulart, A.C., de Oliveira, J.F., Zanao, T.A., Boggio, P.S., et al., 2013. The sertraline versus electrical current therapy for treating depression clinical study (select-TDCS): results of the crossover and follow-up phases. Depress. Anxiety 30, 646–653.
Venkatakrishnan, A., Sandrini, M., 2012. Combining transcranial direct current stimulation and neuroimaging: novel insights in understanding neuroplasticity. J. Neurophysiol. 107, 1–4.
Volpato, C., Piccione, F., Cavinato, M., Duzzi, D., Schiff, S., Foscolo, L., et al., 2013. Modulation of affective symptoms and resting state activity by brain stimulation in a treatment-resistant case of obsessive-compulsive disorder. Neurocase 19, 360–370.
Wagner, T., Valero-Cabre, A., Pascual-Leone, A., 2007. Noninvasive human brain stimulation. Annu. Rev. Biomed. Eng. 9, 527–565.
Whiteford, H.A., Degenhardt, L., Rehm, J., Baxter, A.J., Ferrari, A.J., Erskine, H.E., et al., 2013. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 382, 1575–1586.
Widdows, K.C., Davis, N.J., 2014. Ethical considerations in using brain stimulation to treat eating disorders. Front. Behav. Neurosci. 8.
Wittchen, H.U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jonsson, B., et al., 2011. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur. Neuropsychopharmacol. 21, 655–679.
Wokke, M.E., Talsma, L.J., Vissers, M.E., 2014. Biasing neural network dynamics using non-invasive brain stimulation. Front. Syst. Neurosci. 8, 246.
Wolkenstein, L., Plewnia, C., 2013. Amelioration of cognitive control in depression by transcranial direct current stimulation. Biol. Psychiatry 73, 646–651.

Appendix A.2 Randomised controlled trial of transcranial direct current stimulation (tDCS) in healthy individuals with frequent food cravings (chapter 3)

Appetite 78C (2014) 55–62

Contents lists available at ScienceDirect

Appetite

journal homepage: www.elsevier.com/locate/appet

Research report

The effects of prefrontal cortex transcranial direct current stimulation (tDCS) on food craving and temporal discounting in women with frequent food cravings ☆

Maria Kekic *, Jessica McClelland, Iain Campbell, Steffen Nestler, Katya Rubia, Anthony S. David, Ulrike Schmidt

Institute of Psychiatry, King's College London, 16 De Crespigny Park, London SE5 8AF, UK

ARTICLE INFO

Article history:
Received 11 December 2013
Received in revised form 4 March 2014
Accepted 9 March 2014
Available online 20 March 2014

Keywords:
Transcranial direct current stimulation (tDCS)
Brain stimulation
Food cravings
Obesity
Eating disorders
Temporal discounting (TD)

ABSTRACT

Bulimia nervosa, binge-eating disorder, and some forms of obesity are characterised by compulsive overeating that is often precipitated by food craving. Transcranial direct current stimulation (tDCS) has been used to suppress food cravings, but there is insufficient evidence to support its application in clinical practice. Furthermore, the potential moderating role of impulsivity has not been considered. This study used a randomised within-subjects crossover design to examine whether a 20-minute session of sham-controlled bilateral tDCS to the dorsolateral prefrontal cortex (anode right/cathode left) would transiently modify food cravings and temporal discounting (TD; a measure of choice impulsivity) in 17 healthy women with frequent food cravings. Whether the effects of tDCS on food craving were moderated by individual differences in TD behaviour was also explored. Participants were exposed to food and a film of people eating, and food cravings and TD were assessed before and after active and sham stimulation. Craving for sweet but not savoury foods was reduced following real tDCS. Participants that exhibited more reflective choice behaviour were more susceptible to the anti-craving effects of tDCS than those that displayed more impulsive choice behaviour. No differences were seen in TD or food consumption after real versus sham tDCS. These findings support the efficacy of tDCS in temporarily lowering food cravings and identify the moderating role of TD behaviour.

Introduction

It has been proposed that certain foods – particularly those high in sugar – are addictive, and that obesity and eating disorders, such as bulimia nervosa (BN) and binge-eating disorder (BED), can be conceptualised as forms of addiction (Avena, Rada, & Hoebel, 2009). Food cravings (intense urges to consume particular foods) are thought to precipitate the compulsive overeating that characterises these conditions, and have been positively associated with binge-eating (Ng & Davis, 2013), daily calorie intake (Lafay et al., 2000), BMI (Franken & Muris, 2005), daytime sleep (Landis, Parker, & Dunbar, 2009), and dieting failure (Meule, Westenhöfer, & Kübler, 2011). There is also evidence that excessive craving for sweet foods is associated with drug and alcohol abuse (for a review see Pelchat, 2002).

Extensive behavioural and neurobiological data indicate many commonalities between food craving and drug craving (for a review see Pelchat, 2009). For instance, both lead to foraging and ingestion habits that persist and strengthen despite the threat of negative health and social consequences (Volkow & Wise, 2005) and, furthermore, cravings can predict both relapse to drug taking in abstinent substance users (Rosenberg, 2009) and weight regain after bariatric surgery in obese patients (Odom et al., 2010). The neurotransmitter systems implicated in food craving overlap substantively with those involved in drug craving; for example, exposure to both food and drug craving-provoking stimuli is associated with increased levels of reward circuitry dopaminergic activation in the brain (Blum, Liu, Shriner, & Gold, 2011). Food craving and drug craving are also mediated by shared functional neuroanatomy. Several brain regions appear to be involved (for a review see Tang, Fellows, Small, & Dagher, 2012), but most data suggest that the left, right, or bilateral dorsolateral prefrontal cortex (DLPFC; an area in the prefrontal cortex important for executive functioning) is activated in response to cues that induce both food (Gearhardt et al., 2011; Siep et al., 2009) and drug cravings (Bonson et al., 2002; Hayashi, Ko, Strafella, & Dagher, 2013; Maas et al., 1998). The level of cue-elicited prefrontal activation can predict prospective food intake

☆ *Acknowledgements:* Maria Kekic is supported by an Institute of Psychiatry (IOP) Excellence Studentship. Anthony David and Ulrike Schmidt receive salary support from the National Institute for Health Research (NIHR) Specialist Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and IOP, King's College London.

* Corresponding author.
E-mail address: maria.kekic@kcl.ac.uk (M. Kekic).

http://dx.doi.org/10.1016/j.appet.2014.03.010
0195-6663/

(Cornier, Salzberg, Endly, Bessesen, & Tregellas, 2010) and drug use (Grüsser et al., 2004), and appears to be altered in compulsive overeaters (Schienle, Schäfer, Hermann, & Vaitl, 2009) and drug-addicted individuals (Wexler et al., 2001; Yalachkov, Kaiser, & Naumer, 2009) compared with healthy controls. A deficiency in the prefrontal cortical inhibitory networks might therefore contribute to the pathophysiology of disordered eating and substance use disorders.

A growing number of studies have sought to directly manipulate DLPFC activation as a means of reducing cravings. Two non-invasive brain stimulation (NIBS) methods have been used, both of which are well-tolerated, have minimal side effects, and do not require surgical procedures. Repetitive transcranial magnetic stimulation (rTMS) employs an electromagnetic field generated by a figure-eight coil to suppress (low-frequency) or enhance (high-frequency) cortical excitability in a localised area of the brain (McClelland, Bozhilova, Campbell, & Schmidt, 2013a). Alternatively, transcranial direct current stimulation (tDCS) involves the delivery of a weak electrical current via two surface electrodes; anodal and cathodal tDCS cause excitatory and inhibitory effects on underlying cortical neurons, respectively (McClelland et al., 2013a).

Research has consistently shown that NIBS can reduce drug craving in laboratory settings; cue-provoked cravings for cocaine, alcohol, and nicotine have been transiently lowered with a single session of rTMS or tDCS to the left or right DLPFC (Boggio et al., 2008; Camprodon, Martinez-Raga, Alonso-Alonso, Shih, & Pascual-Leone, 2007; Fregni et al., 2008b; Li et al., 2013; Mishra, Nizamie, Das, & Praharaj, 2010). Emerging evidence indicates that NIBS can also temporarily lower cravings for foods (for reviews see Jansen et al., 2013; McClelland et al., 2013a). In the earliest of these studies, Uher et al. (2005) showed that a single session of high-frequency rTMS to the left DLPFC suppressed cravings in healthy women with frequent food cravings. This finding was later replicated by two studies using bilateral DLPFC tDCS (anode right/cathode left), the former also showing a reduction in calories ingested following active versus sham stimulation (Fregni et al., 2008a; Goldman et al., 2011). The effects of prefrontal cortex modulation have also been investigated in a clinical sample; Van den Eynde et al. (2010) found that high-frequency rTMS to the left DLPFC lowered cue-induced food cravings in patients with a bulimic disorder.

Although the anti-craving effects recorded in these experiments were temporary (the effects of a single session of rTMS or tDCS are expected to last for up to two hours, depending on the parameters used; Nitsche & Paulus, 2001; Hoogendam, Ramakers, & Lazzaro, 2010), it is possible that NIBS delivered over extended periods of time could induce longer-lasting behavioural responses through changes in neuroplasticity. Indeed, interventions comprising multiple sessions of NIBS have shown therapeutic potential for a range of conditions, including BN (Downar, Sankar, Giacobbe, Woodside, & Colton, 2012), anorexia nervosa (McClelland et al., 2013b), and substance use disorder (Politi, Fauci, Santoro, & Smeraldi, 2008). Moreover, rTMS is now an approved second-line treatment for major depressive disorder in the USA. Given that food cravings play a central role in obesity and some eating disorders, the potential for NIBS to enduringly suppress these cravings represents an exciting prospect.

Whilst the tendency to overeat or binge-eat can be influenced by food cravings, Davis, Levitan, Muglia, Bewell, and Kennedy (2004) point out that "human overeating is not just a passive response to . . . powerful physiological drives; it is also about making choices" (p. 929). It is well-established that drug addicts have maladaptive decision-making capabilities (for a review see Dom, Sabbe, Hulstijn, & van den Brink, 2005), and the same applies to compulsive overeaters. Specifically, obese people and patients with BED show steeper rates of temporal discounting (TD) (Davis, Patte, Curtis, & Reid, 2010; Weller, Cook, Avsar, & Cox, 2008) – an experimental proxy of aspects of impulsivity such as temporal foresight and delay of gratification. In the context of eating, these individuals struggle to defer food gratification in the interest of future health or aesthetics. Evidence shows that the capacity for self-control in reward-related decision-making tasks – including TD – depends crucially on DLPFC activity levels (Christakou, Brammer, & Rubia, 2011; Clark, Manes, Antuon, Sahakian, & Robbins, 2003; Hare, Camerer, & Rangel, 2009). Furthermore, reduced prefrontal reactivity during a TD task has been found to predict a greater rate of weight gain in obesity (Kishinevsky et al., 2012). It is possible that NIBS could reduce overeating behaviours by simultaneously suppressing food cravings and improving intertemporal decision-making. Indeed, Figner et al. (2010) showed that low-frequency rTMS delivered to the left DLPFC altered the discounting of delayed rewards in healthy adults. Nevertheless, to our knowledge, the relationship between the DLPFC, food craving, and TD behaviour is yet to be explored.

This study investigated whether bilateral manipulation of the DLPFC with tDCS modulates food craving-related thoughts and behaviours in healthy women who experience frequent food cravings. tDCS was chosen because of its practical advantages over rTMS (Poreisz, Boros, Antal, & Paulus, 2007; Priori, Hallett, & Rothwell, 2009), and because its efficacy in lowering food cravings has been demonstrated in two non-clinical samples comparable to our own (Fregni et al., 2008a; Goldman et al., 2011). Unlike these studies, however, we also included a measure of choice impulsivity. The main aims were to establish whether: (1) one session of sham-controlled tDCS (anode over the right DLPFC and cathode over the left DLPFC) would temporarily reduce food cravings; (2) this session of tDCS would transiently alter TD behaviours; and (3) the effects of tDCS on food cravings are moderated by individual differences in intertemporal decision-making abilities. Based on Fregni et al.'s (2008a) finding, we also speculated that actual food consumption in a free-eating task might decrease following active versus sham stimulation.

Materials and methods

Participants

Healthy female volunteers who self-identified as having frequent food cravings (≥1 per day, assessed by self-report questionnaire) aged 18-60 were recruited from the King's College London (KCL) recruitment webpage. Respondents were screened by phone and were excluded if they: (a) smoked > 10 cigarettes per day; (b) drank > the recommended daily alcohol intake (3–4 units for men and 2–3 units for women; National Health Service, 2013); (c) used illicit drugs; (d) had a current major psychiatric disorder; (e) had a current or past history of an eating disorder; (f) had any significant health problems in the previous 6 months; (g) had a personal or family history of seizures; (h) had a history of stroke; (i) had a history of head injury or neurosurgery; (j) had any implanted metal devices; (k) suffered from frequent or severe headaches; (l) were taking any medications associated with lowered seizure threshold; (m) were pregnant or sexually active and not using contraception; (n) were allergic to any of the foods presented in the study; or (o) gave any threshold answers in the Structured Clinical Interview for Diagnostic and Statistical Manuel (DSM) Axis I Disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 2002).

Twenty-eight women completed the telephone screen and 25 fulfilled all inclusion/exclusion criteria. Of these, 20 completed both study sessions – 4 withdrew before the first visit and 1 experienced skin irritation and so did not return for the second appointment. The data of three participants were excluded due to their responses in baseline assessments completed in the laboratory – two had clinically significant global scores (≥4; Rø, Reas, & Rosenvinge, 2012) on the Eating Disorder Examination Questionnaire (EDE-Q;

Table 1
Baseline characteristics of participants.

Characteristic	Mean	SD	Range
Age	26.41	8.31	19.00–55.00
BMI	23.81	2.60	19.90–29.30
DASS-21 depression	3.88	4.33	0.00–14.00
DASS-21 anxiety	2.12	2.40	0.00–8.00
DASS-21 stress	7.18	4.53	0.00–18.00
Global EDE-Q	1.46	0.98	0.49–3.88
Global FCQ-T	118.47	18.46	91.00–151.00
Cravings per day[a]	3.15	1.36	1.00–5.50
Baseline *k*-value	8.05	9.86	0.91–39.92

SD, standard deviation; BMI, body mass index; DASS-21, 21-item Depression, Anxiety and Stress Scale; EDE-Q, Eating Disorders Examination Questionnaire; FCQ-T, Food Craving Questionnaire-Trait.
[a] Assessed with self-report demographic questionnaire ("How many food cravings do you experience per day?").

Fairburn & Beglin, 1994) and one had moderate scores on all three dimensions of the Depression Anxiety and Stress Scale (DASS-21; Lovibond & Lovibond, 1995). The final sample included in the analyses consisted of 17 females aged 19–55 ($M = 26.41$, $SD = 8.30$) who were predominantly Caucasian (70.6%). Participants reported experiencing an average of 3.15 ($SD = 1.41$, range = 1–5.5) food cravings per day and the majority (82.4%) primarily craved sweet foods. The mean BMI was 23.81 ($SD = 2.60$, range = 19.85–29.28); 70.6% of participants were in the healthy range (18.5–24.9) and 29.4% were overweight (25–25.9) (National Health Service, 2012). All participants were educated to A-level standard or higher. See Table 1 for more participant characteristics.

The study was carried out at the Institute of Psychiatry, KCL (London, UK). Ethical approval was obtained from the KCL Psychiatry, Nursing and Midwifery Research Ethics Subcommittee. All participants provided written informed consent and were debriefed fully at the end of the experiment.

Design and procedure

This study employed a double-blind sham-controlled within-subjects crossover design in which all participants received real and sham tDCS. Order of stimulation was randomised and counterbalanced across participants using STATA® software (to allow for experimenter blinding, real and sham stimulation were encoded with five-digit numbers which were assigned to each session by a third party). An intersession interval (≥48 h) was used to avoid any carryover effects due to stimulation and, where possible, both sessions were held at the same time of day (difference between time of day of real and sham session: $M = 61$ min, $SD = 121$ min).

Upon arrival to the first appointment only, participants completed a battery of baseline assessments (demographic questionnaire, EDE-Q, DASS-21, Food Craving Questionnaire-Trait (FCQ-T; Cepeda-Benito, Gleaves, Williams, & Erath, 2000)). A 10 cm continuous visual analogue scale (VAS) measuring baseline hunger was administered at the start of both sessions, followed by several pre-tDCS measures in the following order: (1) Food Challenge Task (FCT); (2) Food Craving Questionnaire-State (FCQ-S); (3) saliva sample; and (4) TD task. Participants then received a 20-minute tDCS session (real or sham). Immediately after this (post-tDCS), they repeated the pre-tDCS measures in the following order: (1) TD task; (2) FCT; (3) FCQ-S; and (4) saliva sample. Participants then engaged in a free-eating task. At the end of the second appointment only, we evaluated the tolerability of the intervention and the success of the blinding procedure. All instruments used in the protocol have sound psychometric properties.

Food Challenge Task (FCT)

This is a behavioural measure – used to induce and assess food cravings – which was developed and administered previously in our laboratory (Uher et al., 2005; Van den Eynde et al., 2010; Van den Eynde, Guillaume, Broadbent, Campbell, & Schmidt, 2013), and adapted for use in the current study. Two short films (<3 min each) of adults eating energy-dense foods (chocolates, crisps, nuts, and biscuits) were shown to participants consecutively, and the same foods were present in the room. After the films, participants rated their attitude towards food intake and their emotional state on a series of 10 cm continuous VASs measuring appearance, smell, taste, and urge to eat for each food separately, as well as hunger, general urge to eat, general urge to binge, stress, anxiety, tension, and mood. The primary outcome variable in the analyses (global FCT score) was computed by totalling the ratings on all VASs relating to food intake except for hunger. This is because food cravings tend to be hedonically driven and are unrelated to an individual's physiological needs (Davis et al., 2010; Pelchat, Johnson, Chan, Valdez, & Ragland, 2004).

Food Craving Questionnaire-State (FCQ-S)

This is a self-report inventory used to assess food craving as a psychological state in response to specific situations, which was developed for use among average-weight adults (Cepeda-Benito et al., 2000). The instrument contains 15 items organised into 5 subscales. Responses are made on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree), yielding a global score and a score for each dimension.

Hormonal stress response (saliva sample)

To assess whether tDCS had an effect on the hypothalamus–pituitary–adrenal (HPA) axis stress response, we collected salivary cortisol samples. Participants chewed on a 3 × 1 cm inert polymer oral swab (Salivette®) for 1 min, which was then placed into a capped centrifuge tube. Samples were stored at –20°C – where they remain stable for up to 3 months (Garde & Hansen, 2005) – and were analysed for cortisol using competitive immunoassays (Salimetrics® salivary ELISA kits). Data indicate that cortisol measurement with Salivettes® is a reliable prediction method of total and calculated free serum cortisol levels (Poll et al., 2007).

Temporal Discounting (TD) task

Choice impulsivity was assessed with a computerised hypothetical monetary TD task, which measures the degree to which a reward is subjectively discounted in relation to its temporal delay (Rubia, Halari, Christakou, & Taylor, 2009). A monetary task was used because compulsive overeaters appear to have a general tendency to make impulsive choices, which is not specific to choices about food (Manwaring, Green, Myerson, Strube, & Wilfley, 2011). Participants chose between a smaller amount of money (between £0 and £100) available immediately, and a larger amount (always £100) available after 1 week, 1 month, 1 year, or 2 years (25 trials for each delay). The value of the immediate reward was adjusted in an algorithm based on previous choices; this narrowed the range of the immediate values offered until an amount was reached that the participant judged as equivalent to the fixed delayed reward (Richards, Zhang, Mitchell, & de Wit, 1999). This point of subjective equality is referred to as the indifference point. A hyperbolic decay function was fitted to the indifference point for each delay to describe the relationship between the subjective value of a reward as a function of the delay to its presentation. The mathematical expression of this relationship is $V = A/(1 + kD)$, where V is the subjective value of a reward of amount A, D is the delay to reward

presentation, and k is a constant characterising the individual's rate of discounting (Rachlin, Raineri, & Cross, 1991). The value of k is frequently used as the main dependent variable in the TD paradigm, and is considered an experimental proxy of aspects of impulsivity such as temporal foresight and delay of gratification. Participants with larger k-values show greater TD – for them rewards given after a delay lose more subjective value.

Real transcranial direct current stimulation (tDCS)

A single 20-minute session of tDCS was delivered using a neuroConn® DC-STIMULATOR device at a constant current of 2 mA (with a 10-second fade in/out) using two 25 cm^2 surface sponge electrodes soaked in a sterile saline solution (0.9% sodium chloride). At least 50% of this transcranially applied current is expected to enter the brain through the skull (Nitsche et al., 2008). The anode and cathode were placed over the right (F4) and left (F3) DLPFC, respectively. The sites of interest were located using the International EEG 10-20 system. The tDCS parameters used have been shown to be safe in healthy individuals (Iyer et al., 2005) and the charge density was two magnitudes lower than the experimentally determined threshold estimate in rats (Liebetanz et al., 2009). tDCS is generally well-tolerated and is associated with relatively minor side effects; a mild tingling sensation is the most commonly reported adverse effect (Poreisz et al., 2007). We assessed tolerability via salivary cortisol and a 10 cm continuous VAS measuring discomfort during the procedure.

Sham transcranial direct current stimulation (tDCS)

The electrode placement for sham tDCS was the same as for active tDCS; however, the stimulation automatically turned off after 30 s. Participants therefore experienced the initial itching sensation but received no current for the rest of the 20-minute session. Research shows that this method for sham tDCS is reliable and cannot easily be distinguished from real tDCS by participants or investigators (Gandiga, Hummel, & Cohen, 2006). The validity of the sham treatment was assessed by asking participants to guess which session they thought was a placebo, and to rate their confidence in this guess on a 10 cm continuous VAS.

Free-eating task

To measure actual food consumption after real and sham tDCS, weights of foods presented in the FCT were recorded before and after each laboratory session. After the final post-tDCS measure, the experimenter left the room for 3 min and invited the participant to help themselves to any of the foods while they were gone. The percentage eaten was calculated for each food separately and for all foods together.

Results

Statistical analyses were performed using IBM® SPSS® software (Version 20). For variables with normally distributed data, the effects of active versus sham tDCS were evaluated using two-way 2 (stimulation: real vs. sham) × 2 (timepoint: pre-tDCS vs. post-tDCS) repeated measures ANOVAs, whereby a significant stimulation × timepoint interaction indicated a difference in the effect that real and sham tDCS had on pre-tDCS scores. Where data were not normally distributed, non-parametric alternatives were employed. All statistical tests were two-tailed and the level of significance was set at $\alpha = 0.05$.

Food cravings and tDCS

When compared with sham stimulation, real stimulation did not alter global FCT scores [$F(1, 16) = 0.74$, *ns*]. There was a significant stimulation × timepoint interaction for global FCQ-S score [$F(1, 16) = 5.02$, $P < .05$] in the opposite direction to that expected; pre-tDCS scores were lowered more by sham ($M = -11.32\%$, $SD = 21.12\%$) than by real stimulation ($M = -1.94\%$, $SD = 21.36\%$). However, this finding is largely attributable to scores on FCQ-S subscale 5 (craving as a physiological state) as the global FCQ-S interaction term was not significant when this subscale was excluded from the analysis [$F(1, 16) = 3.19$, *ns*].

Food cravings for specific food groups and tDCS

To examine the effect of tDCS on cravings for specific food groups, we analysed FCT ratings (appearance, smell, taste, urge to eat) for sweet (chocolate and biscuits) and savoury (crisps and nuts) foods separately. A significant stimulation × timepoint interaction was observed for sweet [$F(1, 16) = 4.59$, $P < .05$] but not savoury foods [$F(1, 16) = 2.20$, *ns*]. Cravings for sweet foods were reduced more by real ($M = -13.31\%$, $SD = 34.73\%$) than by sham tDCS ($M = -6.06\%$, $SD = 29.86\%$), whilst cravings for savoury foods were lowered by comparable amounts in both conditions (real: $M = -9.29\%$, $SD = 36.84\%$, sham: $M = -10.30\%$, $SD = 30.46\%$) (Fig. 1).

Temporal discounting and tDCS

Since k-values on the TD task were not normally distributed, the effect of tDCS on intertemporal choice behaviour was evaluated using paired-samples Wilcoxon signed-rank tests. Post-tDCS k-values did not differ significantly from pre-tDCS k-values following real [$z = -0.45$, *ns*] or sham stimulation [$z = -0.31$, *ns*].

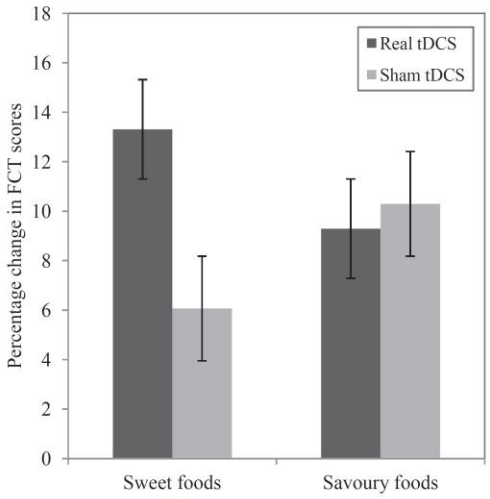


Fig. 1. Mean percentage change in Food Challenge Task scores (appearance, smell, taste, urge to eat) for sweet and savoury foods in real and sham tDCS conditions. Error bars represent ± SE.

Interaction between temporal discounting, food cravings, and tDCS

To establish whether the effects of tDCS on food cravings were moderated by individual differences in intertemporal decision-making abilities, we performed the analyses with baseline *k*-value (calculated as the mean of the two pre-tDCS *k*-values) as a covariate. Results showed a significant stimulation × timepoint interaction for global FCT score [$F(1, 15) = 4.82$, $P < .05$]; after controlling for baseline *k*-value there was a sharper decrease in global FCT scores following real tDCS than following sham tDCS. In addition, the stimulation × timepoint interaction for global FCQ-S score was no longer significant [$F(1, 15) = 0.18$, *ns*].

There was also a significant stimulation × timepoint × baseline *k*-value interaction for global FCT score [$F(1, 15) = 5.12$, $P < .05$] and global FCQ-S score [$F(1, 15) = 5.60$, $P < .05$]. Participants with lower baseline *k*-values – and greater intertemporal decision-making abilities – were more susceptible to the anti-craving effects of active tDCS. Conversely, baseline *k*-value did not moderate the effects that sham tDCS had on food cravings. To illustrate this graphically, we divided participants into two groups according on their baseline *k*-value; participants with baseline *k*-values in the first or second quartiles ($n = 9$) were classified as showing low TD (more reflective choice behaviour) whilst those with baseline *k*-values in the third or fourth quartiles ($n = 8$) were categorised as showing high TD (more impulsive choice behaviour) (Fig. 2).

Actual food consumption and tDCS

Values for the amount of food consumed during the free-eating task were not normally distributed, and were therefore analysed using paired-samples Wilcoxon signed-rank tests. Results showed no significant difference in the proportion of chocolate, crisps, nuts, biscuits, or total food ingested after real versus sham tDCS [$zs < -1.04$, $ps > .30$]. These results were not confounded by baseline hunger which was stable across the two conditions [$t(16) = -0.67$, *ns*].

Success of blinding procedure

Participants were not able to distinguish real stimulation from sham stimulation at a rate better than chance [$\chi^2(1) = 2.88$, *ns*]. Furthermore, the mean confidence rating for this guess on a 10 cm continuous VAS was 5.04 ($SD = 3.12$, range = 0.0–9.7), indicating that participants were not particularly certain that their guess was accurate. The order in which participants received real and sham stimulation did not affect their ability to identify the placebo session [$P = .29$; Fisher's exact test].

Tolerability and safety of tDCS

One participant withdrew from the study after the first appointment due to skin irritation at the site of stimulation. Another participant reported developing a slight headache following active tDCS which subsided without treatment. Overall, the intervention was well-tolerated and participants reported experiencing minimal discomfort (10 cm VAS: $M = 2.64$, $SD = 2.51$, range = 0–7.7). When compared with sham tDCS, real tDCS did not have any adverse effects on the HPA axis stress response [$F(1, 15) = 0.29$, *ns*] and did not alter self-reported stress, anxiety, tension, or mood [$Fs < 0.55$, $ps > .47$].

Order effects

There was evidence of an order effect whereby, following real stimulation, participants allocated to the real/sham condition displayed a sharp decrease in global FCT scores whereas those in the sham/real condition showed a marginal increase in scores [$F(1, 15) = 7.17$, $P < .05$]. Participants who received real tDCS first ($n = 8$) did not differ significantly from those who received sham tDCS first ($n = 9$) in any baseline measures [$Fs < 3.89$, $ps > .08$].

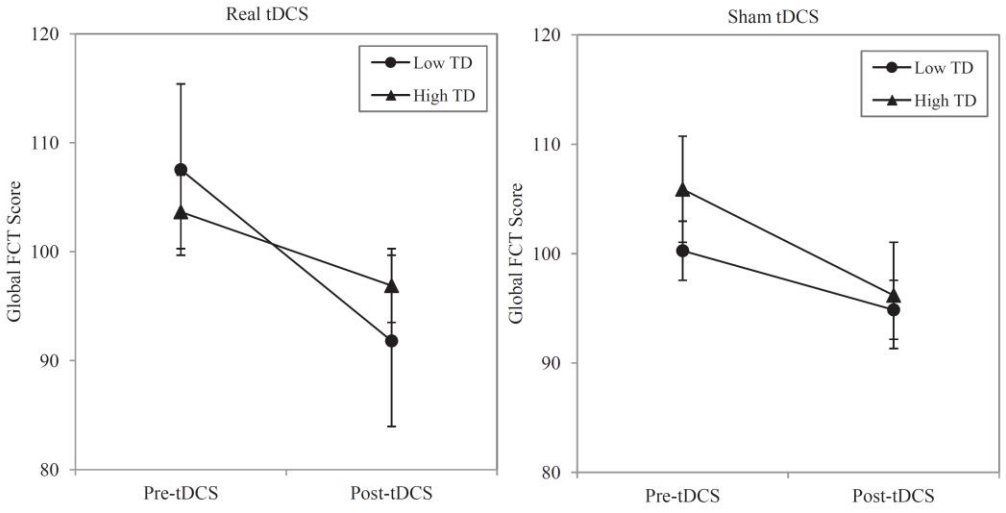


Fig. 2. Mean pre- and post-tDCS global Food Challenge Task scores for participants showing high and low temporal discounting in real and sham tDCS conditions.

Discussion

The present study investigated the effects of a single session of sham-controlled tDCS (anode over the right DLPFC, cathode over the left DLPFC) on food cravings, intertemporal choice behaviour, and actual food consumption in healthy women with frequent food cravings. The key findings were that tDCS reduced cravings for sweet but not savoury foods, and that participants who exhibited more reflective choice behaviour were more susceptible to the anti-craving effects of tDCS than those who displayed more impulsive choice behaviour.

The observed decrease in craving for sweet foods is consistent with numerous accounts of prefrontal cortex tDCS transiently lowering food and drug cravings (Boggio et al., 2008; Fregni et al., 2008a, 2008b; Goldman et al., 2011), and provides evidence that food craving is associated with DLPFC activity. This brain region is thought to regulate cravings by integrating information relating to cues, cravings, motivation, and expectancy (McBride, Barrett, Kelly, Aw, & Dagher, 2006). By combining rTMS with functional magnetic resonance imaging (fMRI), Hayashi et al. (2013) formulated a two-stage model of cue reactivity whereby the medial orbitofrontal cortex (mOFC) encodes the subjective value of the drug (or food) and the DLPFC incorporates intertemporal availability and cue information to modulate the presumed mOFC value signal.

The mechanisms by which DLPFC stimulation lowers cravings are unknown, although data suggest that reduced function in the right prefrontal cortex may lead to overeating (Alonso-Alonso & Pascual-Leone, 2007). Interestingly, however, NIBS appears to suppress cravings even when the right DLPFC is inhibited and/or the left DLPFC is excited (Boggio et al., 2008; Fregni et al., 2008a, 2008b; Uher et al., 2005; Van den Eynde et al., 2010). It has therefore been proposed that state craving depends on a bilateral balance between left and right DLPFC activity and that any disruption to this balance will cause cravings to subside (Boggio et al., 2008). DLPFC modulation might also lead to craving inhibition by indirectly altering the activity level of the mOFC.

That tDCS suppressed cravings for sweet but not savoury foods is in approximate agreement with Goldman et al.'s (2011) findings, and provides an explanation as to why global FCQ-S and global FCT scores were not reduced by tDCS. It is possible that the mechanisms underlying cravings for sweet and savoury foods are different; several lines of evidence support this interpretation. Firstly, the concept of sweet food addiction is frequently likened to drug addiction (e.g. Avena, Rada, & Hoebel, 2008), whereas parallels have not been drawn between drug addiction and addiction to savoury foods. Secondly, chocolate contains several biologically active constituents – which are not found in savoury foods – that can cause psychological sensations comparable to those of other addictive substances (Bruinsma & Taren, 1999). Thirdly, sweet foods generally contain higher sugar concentrations than savoury foods, and sugar is known to have addictive potential because it releases opioids and dopamine (Avena et al., 2008). Finally, ample data – including those in this study – indicate that cravings for sweet foods are stronger and more prevalent than cravings for savoury foods (Hill, 2007; Yanovski, 2003).

The present study demonstrates that inter-individual differences in intertemporal decision-making abilities moderate the anti-craving effects of prefrontal cortex tDCS. Specifically, participants who exhibited more impulsive choice behaviours showed a smaller reduction in cravings following active stimulation than those who displayed more reflective choice behaviours. This is unsurprising since individuals with a strong tendency to devalue delayed rewards are expected to hold particularly disinhibited attitudes towards food intake (Davis et al., 2010). Unlike Figner et al. (2010), we did not observe significant changes in TD following DLPFC modulation. It may be that an individual's ability to delay gratification cannot be easily modified with NIBS; indeed, only one study has demonstrated otherwise and, moreover, the capacity for adaptive intertemporal decision-making is not a capricious psychological state but rather a stable personality trait (Davis et al., 2010).

In our study, real versus sham tDCS did not affect the amount of food consumed in the free-eating task. Although Fregni et al. (2008a) reported reduced caloric ingestion following active stimulation, Goldman et al. (2011) did not replicate this result. It is possible that the observed reduction in self-reported craving did not translate into an equipollent reduction in food consumption because the free-eating session lacked ecological validity; eating behaviours displayed in this task are unlikely to mirror those engaged in on a daily basis. Goldman et al. (2011) suggested instead performing "a natural observation of food consumption during a mealtime later in the day or the following day" (p. 745); however, the tDCS parameters used are not expected to have such a lasting effect. It might therefore prove more beneficial to revise the experimental free-eating task to improve its generalisability; for example, it could take place in a more natural setting and its length could be increased.

This study has some limitations; for example, we observed an order effect whereby real tDCS only reduced food cravings for participants who received real stimulation during their first session. One explanation for this draws on the finding that cue-induced craving for cigarettes was dramatically increased when people were told they could smoke immediately after testing (Hayashi et al., 2013). In our study, participants were not informed prior to testing that they would be given *ad libitum* access to a selection of foods; therefore, they would have only anticipated the free-eating task during their second visit, once they were familiarised with the experimental procedure. This anticipation might have potentiated cravings in the second session, making them less susceptible to modulation by tDCS. We did not ask participants to fast prior to their scheduled sessions. Although hunger is not a necessary prerequisite for food craving (Pelchat et al., 2004), similar studies have required that participants refrain from eating and drinking (except water) for several hours before testing (Goldman et al., 2011; Uher et al., 2005; Van den Eynde et al., 2010). Nevertheless, our results showed that baseline hunger was stable across conditions. We also did not collect data on menstrual phase despite evidence that it influences food craving (Davidsen, Vistisen, & Astrup, 2007); however, not all studies of NIBS and food craving have addressed this issue (Fregni et al., 2008a; Van den Eynde et al., 2010). In addition, we did not control for individual differences in IQ or income which may influence TD of monetary rewards (de Wit, Flory, Acheson, McCloskey, & Manuck, 2007; Green, Myerson, Lichtman, Rosen, & Fry, 1996). A final limitation is that we did not include an anode left/cathode right tDCS condition, which would have helped to clarify whether there is a hemispheric laterality for food craving.

The present research has some important implications. Although the anti-craving effects observed here were presumably only temporary, it is possible that NIBS delivered over longer periods of time could elicit more sustained reductions in food craving. tDCS is an appealing technique because it is inexpensive, easy to administer, non-invasive, and painless. Future research should evaluate the therapeutic potential of tDCS for eliminating problematic overeating and binge-eating behaviours by analysing the effects of repeated DLPFC stimulation. The inter-individual differences we detected in a participant's susceptibility to the anti-craving effects of stimulation suggest that, if developed into a treatment for compulsive overeating, tDCS might be less effective for patients with poorer intertemporal decision-making abilities. It may be possible to teach these individuals more adaptive strategies to prepare them for a tDCS intervention.

In summary, our data contribute to the growing body of literature demonstrating that a single session of active tDCS to the DLPFC can temporarily suppress food craving. Our results support those

of Fregni et al. (2008a) and Goldman et al. (2011), and extend them by suggesting that tDCS has a stronger inhibitory effect on craving for sweet foods than on craving for savoury foods. We have also shown that individuals who exert more reflective choice behaviours are more susceptible to the anti-craving effects of tDCS than those who display more impulsive choice behaviours. The potential for DLPFC neuromodulation to transiently alter intertemporal choice behaviour was not supported here and warrants further investigation.

References

Alonso-Alonso, M., & Pascual-Leone, A. (2007). The right brain hypothesis for obesity. *The Journal of the American Medical Association*, *297*, 1819–1822.

Avena, N. M., Rada, P., & Hoebel, B. G. (2008). Evidence for sugar addiction. Behavioural and neurochemical effects of intermittent, excessive sugar intake. *Neuroscience and Biobehavioural Reviews*, *32*, 20–29.

Avena, N. M., Rada, P., & Hoebel, B. G. (2009). Sugar and fat bingeing have notable differences in addictive-like behaviour. *The Journal of Nutrition*, *139*, 623–628.

Blum, K., Liu, Y., Shriner, R., & Gold, M. S. (2011). Reward circuitry dopaminergic activation regulates food and drug craving behavior. *Current Pharmaceutical Design*, *17*, 1158–1167.

Boggio, P. S., Sultani, N., Fecteua, S., Merabet, L., Mecca, T., Pascual-Leone, A., et al. (2008). Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving. A double-blind, sham-controlled study. *Drug and Alcohol Dependence*, *92*, 55–60.

Bonson, K., Grant, S., Comtoreggi, C., Links, J., Metcalfe, J., Weyl, H., et al. (2002). Neural systems and cue-induced cocaine craving. *Neuropsychopharmacology*, *26*, 376–386.

Bruinsma, K., & Taren, D. L. (1999). Chocolate. Food or drug? *Journal of the American Dietetic Association*, *99*, 1249–1256.

Camprodon, J. A., Martinez-Raga, J., Alonso-Alonso, M., Shih, M. C., & Pascual-Leone, A. (2007). One session of high frequency repetitive transcranial magnetic stimulation (rTMS) to the right prefrontal cortex transiently reduces cocaine craving. *Drug and Alcohol Dependence*, *86*, 91–94.

Cepeda-Benito, A., Gleaves, D. H., Williams, T. L., & Erath, S. A. (2000). The development and validation of the state and trait food craving questionnaires. *Behaviour Therapy*, *31*, 151–173.

Christakou, A., Brammer, M., & Rubia, K. (2011). Maturation of limbic corticostriatal activation and connectivity associated with developmental changes in temporal discounting. *Neuroimage*, *54*, 1344–1354.

Clark, L., Manes, F., Antuon, N., Sahakian, B. J., & Robbins, T. W. (2003). The contributions of lesion laterality and lesion volume to decision-making impairment following frontal lobe damage. *Neuropsychologia*, *41*, 1474–1483.

Cornier, M. A., Salzberg, A. K., Endly, D. C., Bessesen, D. H., & Tregellas, J. R. (2010). Sex-based differences in the behavioural and neural responses to food. *Physiology & Behavior*, *99*, 538–543.

de Wit, H., Flory, J. D., Acheson, A., McCloskey, M., & Manuck, S. B. (2007). IQ and nonplanning impulsivity are independently associated with delay discounting in middle-aged adults. *Personality and Individual Differences*, *42*, 111–121.

Davidsen, L., Vistisen, B., & Astrup, A. (2007). Impact of the menstrual cycle on determinants of energy balance. A putative role in weight loss attempts. *International Journal of Obesity*, *31*, 1777–1785.

Davis, C., Levitan, R. D., Muglia, P., Bewell, C., & Kennedy, J. L. (2004). Decision-making deficits and overeating. A risk model for obesity. *Obesity Research*, *12*, 929–935.

Davis, C., Patte, K., Curtis, C., & Reid, C. (2010). Immediate pleasures and future consequences. A neurological study of binge eating and obesity. *Appetite*, *54*, 208–213.

Dom, G., Sabbe, B., Hulstijn, W., & van den Brink, W. (2005). Substance use disorders and the orbitofrontal cortex. Systematic review of behavioural decision-making and neuroimaging studies. *The British Journal of Psychiatry*, *187*, 209–220.

Downar, J., Sankar, A., Giacobbe, P., Woodside, B., & Colton, P. (2012). Unanticipated rapid remission of refractory bulimia nervosa, during high-dose repetitive transcranial magnetic stimulation of the dorsomedial prefrontal cortex. A case report. *Frontiers in Psychiatry*, *3*, 1–5.

Fairburn, C. G., & Beglin, S. J. (1994). Assessment of eating disorders. Interview or self-report questionnaire? *International Journal of Eating Disorders*, *16*, 363–370.

Figner, B., Knoch, D., Johnson, E. J., Krosch, A. R., Lisanby, S. H., Fehr, E., et al. (2010). Lateral prefrontal cortex and self-control in intertemporal choice. *Nature Neuroscience*, *13*, 538–539.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (2002). *Structured clinical interview for DSM-IV-TR axis I disorders, research version, non-patient edition (SCID-I/NP)*. New York: Biometrics Research.

Franken, I., & Muris, P. (2005). Individual differences in reward sensitivity are related to food craving and relative body weight in healthy women. *Appetite*, *45*, 198–201.

Fregni, F., Fernanda, O., Pedrosa, W., Fecteau, S., Tome, F., Nitsche, M., et al. (2008a). Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. *Appetite*, *51*, 34–41.

Fregni, F., Liguori, P., Fecteau, S., Nitsche, M. A., Pascual-Leone, A., & Boggio, P. S. (2008b). Cortical stimulation of the prefrontal cortex with transcranial direct current stimulation reduces cue-provoked smoking craving. A randomised, sham-controlled study. *The Journal of Clinical Psychiatry*, *69*, 32–40.

Gandiga, P. C., Hummel, F. C., & Cohen, L. G. (2006). Transcranial DC stimulation (tDCS). A tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical Neurophysiology*, *117*, 845–850.

Garde, A. H., & Hansen, A. M. (2005). Long-term stability of salivary cortisol. *Scandinavian Journal of Clinical and Laboratory Investigation*, *65*, 433–436.

Gearhardt, A. N., Yokum, S., Orr, P. T., Stice, E., Corbin, W. R., & Brownell, K. D. (2011). Neural correlates of food addiction. *Archives of General Psychiatry*, *68*, 1–9.

Goldman, R. L., Borckardt, J. J., Frohman, H. A., O'Neil, P. M., Madan, A., Campbell, L. K., et al. (2011). Prefrontal cortex transcranial direct current stimulation (tDCS) temporarily reduces food cravings and increases the self-reported ability to resist food in adults with frequent food craving. *Appetite*, *56*, 741–746.

Green, L., Myerson, J., Lichtman, D., Rosen, S., & Fry, A. (1996). Temporal discounting in choice between delayed rewards. The role of age and income. *Psychology and Aging*, *11*, 79–84.

Grüsser, S. M., Wrase, J., Klein, S., Hermann, D., Smolka, M. N., Ruf, M., et al. (2004). Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. *Psychopharmacology*, *175*, 296–302.

Hare, T. A., Camerer, C. F., & Rangel, A. (2009). Self-control in decision-making involves modulation of the vmPFC valuation system. *Science*, *324*, 646–648.

Hayashi, T., Ko, J. H., Strafella, A. P., & Dagher, A. (2013). Dorsolateral prefrontal and orbitofrontal cortex interactions during self-control of cigarette craving. *Proceedings of the National Academy of Sciences*, *110*, 4422–4427.

Hill, A. J. (2007). Symposium on molecular mechanisms and psychology of food intake. The psychology of food craving. *Proceedings of the Nutrition Society*, *66*, 277–285.

Hoogendam, J. M., Ramakers, G. M., & Lazzaro, V. D. (2010). Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimulation*, *3*, 95–118.

Iyer, M. B., Mattu, U., Grafman, J., Lomarev, M., Sato, S., & Wasserman, E. M. (2005). Safety and cognitive effect of frontal DC brain polarisation in healthy individuals. *Neurology*, *64*, 872–875.

Jansen, J. M., Daams, J. G., Koeter, M. W., Veltman, D. J., van den Brink, W., & Groudiaan, A. E. (2013). Effects of non-invasive neurostimulation on craving. A meta-analysis. *Neuroscience and Biobehavioral Reviews*, *37*, 2472–2480.

Kishinevsky, F. I., Cox, J. E., Murdaugh, D. L., Stoeckel, L. E., Cook, E. W., & Weller, R. E. (2012). fMRI reactivity on a delay discounting task predicts weight gain in obese women. *Appetite*, *58*, 582–592.

Lafay, L., Thomas, F., Mennen, L., Charles, M. A., Eschwege, E., Borys, J. M., et al. (2000). Gender differences in the relation between food cravings and mood in an adult community. Results from the Fleurbaix Laventie Ville Santé study. *International Journal of Eating Disorders*, *29*, 195–204.

Landis, A. M., Parker, K. P., & Dunbar, S. B. (2009). Sleep, hunger, satiety, food cravings, and caloric intake in adolescents. *Journal of Nursing Scholarship*, *41*, 115–123.

Li, X., Hartwell, K. J., Owens, M., LeMatty, T., Borckardt, J. J., Hanlon, C. A., et al. (2013). Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex reduces nicotine cue craving. *Biological Psychiatry*, *73*, 714–720.

Liebetanz, D., Koch, R., Mayenfels, S., König, F., Paulus, W., & Nitsche, M. A. (2009). Safety limits of cathodal transcranial direct current stimulation in rats. *Clinical Neurophysiology*, *120*, 1161–1167.

Lovibond, S. H., & Lovibond, P. F. (1995). *Manual for the depression anxiety and stress scales* (2nd ed.). Sydney, NSW: Psychology Foundation.

Maas, L. C., Lukas, S. E., Kaufman, M. J., Weiss, R. D., Daniels, S. L., Rogers, V. W., et al. (1998). Functional magnetic resonance imaging of human brain activation during cue-induced cocaine craving. *The American Journal of Psychiatry*, *155*, 124–126.

Manwaring, J. L., Green, L., Myerson, J., Strube, M. J., & Wilfley, D. E. (2011). Discounting of various types of rewards by women with and without binge eating disorder. Evidence for general rather than specific differences. *The Psychological Record*, *61*, 561–582.

McBride, D., Barrett, S. P., Kelly, J. T., Aw, A., & Dagher, A. (2006). Effects of expectancy and abstinence on the neural response to smoking cues in cigarette smokers. An fMRI study. *Neuropsychopharmacology*, *31*, 2728–2738.

McClelland, J., Bozhilova, N., Campbell, I., & Schmidt, U. (2013a). A systematic review of the effects of neuromodulation on eating and body weight. Evidence from human and animal studies. *European Eating Disorders Review*, *21*, 436–455.

McClelland, J., Bozhilova, N., Nestler, S., Campbell, I., Jacob, S., Johnson-Sabine, E., et al. (2013b). Improvements in symptoms following neuronavigated repetitive transcranial magnetic stimulation (rTMS) in severe and enduring anorexia nervosa. Findings from two case studies. *European Eating Disorders Review*, *21*, 500–506.

Meule, A., Westenhöfer, J., & Kübler, A. (2011). Food cravings mediate the relationship between rigid, but not flexible control of eating behavior and dieting success. *Appetite*, *57*, 582–584.

Mishra, B. R., Nizamie, S. H., Das, B., & Praharaj, S. K. (2010). Efficacy of repetitive transcranial magnetic stimulation in alcohol dependence. A sham-controlled study. *Addiction (Abingdon, England)*, *105*, 49–55.

National Health Service. (2012). *What's your BMI?* <http://www.nhs.uk/Livewell/loseweight/Pages/BodyMassIndex.aspx> Accessed 19th March 2014.

National Health Service. (2013). *Alcohol units*. <http://www.nhs.uk/Livewell/alcohol/Pages/alcohol-units.aspx> Accessed 19th March 2014.

Ng, L., & Davis, C. (2013). Cravings and food consumption in binge eating disorder. *Eating Behaviors*, *14*, 472–475.

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., et al. (2008). Transcranial direct current stimulation. State of the art 2008. *Brain Stimulation*, *1*, 206–223.
Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*, *57*, 1899–1901.
Odom, J., Zalesin, K. C., Washington, T. L., Miller, W. W., Hakmeh, B., Zaremba, D. L., et al. (2010). Behavioural predictors of weight regain after bariatric surgery. *Obesity Surgery*, *20*, 349–356.
Pelchat, M. L. (2002). Of human bondage. Food craving, obsession, compulsion, and addiction. *Physiology and Behavior*, *76*, 347–352.
Pelchat, M. L. (2009). Food addiction in humans. *The Journal of Nutrition*, *139*, 620–622.
Pelchat, M. L., Johnson, A., Chan, R., Valdez, J., & Ragland, D. (2004). Images of desire. Food-craving activation during fMRI. *Neuroimage*, *23*, 1486–1493.
Politi, E., Fauci, E., Santoro, A., & Smeraldi, E. (2008). Daily sessions of transcranial magnetic stimulation to the left prefrontal cortex gradually reduce cocaine craving. *The American Journal on Addictions*, *17*, 345–346.
Poll, E. M., Kreitschmann-Andermahr, I., Langejuergen, Y., Stanzel, S., Gilsbach, J. M., Gressner, A., et al. (2007). Saliva collection method affects predictability of serum cortisol. *Clinica Chimica Acta*, *382*, 15–19.
Poreisz, C., Boros, K., Antal, A., & Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Research Bulletin*, *72*, 208–214.
Priori, A., Hallett, M., & Rothwell, J. C. (2009). Repetitive transcranial magnetic stimulation or transcranial direct current stimulation? *Brain Stimulation*, *2*, 241–245.
Rachlin, H., Raineri, A., & Cross, D. (1991). Subjective probability and delay. *Journal of the Experimental Analysis of Behavior*, *55*, 233–244.
Richards, J. B., Zhang, L., Mitchell, S. H., & de Wit, H. (1999). Delay or probability discounting in a model of impulsive behaviour. Effect of alcohol. *Journal of the Experimental Analysis of Behaviour*, *71*, 121–143.
Rosenberg, H. (2009). Clinical and laboratory assessment of the subjective experience of drug craving. *Clinical Psychology Review*, *29*, 519–534.
Rø, Ø., Reas, D. L., & Rosenvinge, J. (2012). The impact of age and BMI on Eating Disorder Examination Questionnaire (EDE-Q) scores in a community sample. *Eating Behaviours*, *13*, 158–161.
Rubia, K., Halari, R., Christakou, A., & Taylor, E. (2009). Impulsiveness as a timing disturbance. Neurocognitive abnormalities in attention-deficit hyperactivity disorder during temporal processes and normalisation with methylphenidate. *Philosophical Transactions of the Royal Society*, *364*, 1919–1931.
Schienle, A., Schäfer, A., Hermann, A., & Vaitl, D. (2009). Binge-eating disorder. Reward sensitivity and brain activation to images of food. *Biological Psychiatry*, *65*, 654–661.
Siep, N., Roefs, A., Roebroeck, A., Havemans, R., Bonte, M., & Jansen, A. (2009). Hunger is the best spice. An fMRI study of the effects of attention, hunger and calorie content on food reward processing in the amygdala and orbitofrontal cortex. *Behavioural Brain Research*, *198*, 149–158.
Tang, D. W., Fellows, L. K., Small, D. M., & Dagher, A. (2012). Food and drug cues activate similar brain regions. A meta-analysis of functional MRI studies. *Physiology & Behavior*, *106*, 317–324.
Uher, R., Yoganathan, D., Mogg, A., Eranti, S. V., Treasure, J., Campbell, I. C., et al. (2005). Effect of left prefrontal repetitive transcranial magnetic stimulation on food craving. *Biological Psychiatry*, *58*, 840–842.
Van den Eynde, F., Claudino, A. M., Mogg, A., Horrell, L., Stahl, D., Ribeiro, W., et al. (2010). Repetitive transcranial magnetic stimulation reduces cue-induced food craving in bulimic disorders. *Biological Psychiatry*, *67*, 793–795.
Van den Eynde, F., Guillaume, S., Broadbent, H., Campbell, I., & Schmidt, U. (2013). Repetitive transcranial magnetic stimulation in anorexia nervosa. A pilot study. *European Psychiatry*, *28*, 98–101.
Volkow, N. D., & Wise, R. A. (2005). How can drug addiction help us understand obesity? *Nature Neuroscience*, *8*, 555–560.
Weller, R. E., Cook, E. W., III, Avsar, K. B., & Cox, J. E. (2008). Obese women show greater delay discounting than healthy-weight women. *Appetite*, *51*, 563–569.
Wexler, B. E., Gottschalk, C. H., Fulbright, R. K., Prohovnik, I., Lacadie, C. M., Rounsaville, B. J., et al. (2001). Functional magnetic resonance imaging of cocaine craving. *The American Journal of Psychiatry*, *158*, 86–95.
Yalachkov, Y., Kaiser, J., & Naumer, M. J. (2009). Brain regions related to tool use and action knowledge reflect nicotine dependence. *The Journal of Neuroscience*, *29*, 4922–4929.
Yanovski, S. (2003). Sugar and fat. Cravings and aversions. *The Journal of Nutrition*, *133*, 835–837.

Appendix A.3 Cross-sectional temporal discounting study (chapter 4)

BRIEF REPORT

Increased Temporal Discounting in Bulimia Nervosa

Maria Kekic, MSc[†]*
Savani Bartholdy, MSc[†]
Jiumu Cheng, MSc
Jessica McClelland, PhD
Elena Boysen, MSc
Peter Musiat, PhD
Owen G. O'Daly, PhD
Iain C. Campbell, DSc
Ulrike Schmidt, MD, PhD, FRCPsych

ABSTRACT

Objective: There is evidence that people with eating disorders display altered intertemporal choice behavior (the degree of preference for immediate rewards over delayed rewards). Compared to healthy controls (HC), individuals with anorexia nervosa and binge-eating disorder show decreased and increased rates of temporal discounting (TD; the devaluation of delayed rewards), respectively. This is the first study to investigate TD in people with bulimia nervosa (BN).

Method: Thirty-nine individuals with BN (2 men) and 53 HC (9 men) completed a hypothetical monetary TD task. Over 80 binary choices, participants chose whether they would prefer to receive a smaller amount of money available immediately or a larger amount available in 3 months. Self-reported ability to delay gratification (the behavioral opposite of TD) was also measured.

Results: Individuals with BN showed greater TD (i.e., a preference for smaller-sooner rewards) and a decreased self-reported capacity to delay gratification relative to HC. Experimental groups did not differ in age, gender ratio, or BMI.

Discussion: Increased rates of TD may contribute to some of the core symptoms of BN that appear to involve making choices between immediate and delayed rewards (i.e., binge-eating and compensatory behaviors). Altered intertemporal choice behavior could therefore be a relevant target for intervention in this patient group. © 2016 Wiley Periodicals, Inc.

Keywords: bulimia nervosa; temporal discounting; impulsivity; reward

(Int J Eat Disord 2016; 00:000-000)

Introduction

The pathophysiology of bulimia nervosa (BN) is poorly understood and strong evidence to guide treatment is lacking.[1] Exploration of neurocognition in BN has the potential to elucidate mechanisms underpinning associated behavioral abnormalities, and to promote the development of tailored therapeutic interventions.

Several neuropsychological difficulties have been observed in BN.[2] For example, individuals with BN, as well as other eating disorders (EDs; anorexia nervosa [AN] and binge-eating disorder [BED]), have an increased preference for risky and disadvantageous choices in a context of uncertainty.[3] There is also evidence that patients with EDs make maladaptive intertemporal choices. A reward arriving sooner is often more appealing than one arriving later, even when the later reward is larger. Thus, individuals discount the value of delayed outcomes—a phenomenon known as temporal discounting (TD). This tendency to devalue future rewards appears to be accentuated in BED (increased TD)[4] and diminished in AN (decreased TD),[5] which may underlie the disinhibited and restrictive eating that characterize these disorders. This study investigated whether individuals with BN display altered rates of TD and differences in the self-reported capacity to delay gratification relative to healthy controls (HC).

Material and Methods

Participants

Participants were men and women ≥18 years with BN or no current/previous diagnosis of any psychiatric

Accepted 19 May 2016
Maria Kekic and Savani Bartholdy share Joint first authorship.
Maria Kekic is supported by an Institute of Psychiatry, Psychology and Neuroscience/Medical Research Council Excellence Studentship. Savani Bartholdy is supported by a studentship awarded by the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre (BRC) at South London and Maudsley (SLaM) NHS Foundation Trust and KCL. Jessica McClelland is supported by the NIHR Mental Health BRC at SLaM NHS Foundation Trust and KCL. Owen O'Daly receives salary support from an NIHR Infrastructure grant for the Wellcome Trust/KCL Clinical Research Facility. Ulrike Schmidt and Iain Campbell receive salary support from the NIHR Mental Health BRC at SLaM NHS Foundation Trust and KCL. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.
*Correspondence to: M. Kekic, E-mail: maria.kekic@kcl.ac.uk
Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom
Published online 00 Month 2016 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/eat.22571

disorder (HC): their data were pooled from two larger studies conducted by our group (currently in preparation for publication). Patients with BN were recruited via online advertisements on the King's College London (KCL) and Beat™ research recruitment webpages and through the South London and Maudsley NHS Foundation Trust ED Outpatient Service, while HC responded to online and poster advertisements at KCL. Group classification was established via self-report and checked over email/telephone: DSM-V BN diagnosis was confirmed using an edited version of the Eating Disorder Diagnostic Scale (EDDS),[6] and the absence of a psychiatric disorder in HC was confirmed using the EDDS and the Structured Clinical Interview for DSM-IV Axis I Disorders Screening Module.[7]

One hundred and thirty participants (BN = 55; HC = 75) completed the screening and 122 (BN = 52; HC = 70) were eligible for inclusion. Of these, 92 (BN = 39; HC = 53) completed the study and were included in the analyses.

The two larger studies were approved by the KCL Psychiatry, Nursing and Midwifery Research Ethics Subcommittee and the London City Road & Hampstead Research Ethics Committee. Participants gave informed consent prior to taking part and were compensated for their time.

Procedure

Full procedural details are provided in Appendix A. All participants attended a testing session at the Institute of Psychiatry, Psychology & Neuroscience, KCL. Study procedures undertaken prior to the TD task were comparable between the two studies: both involved providing written consent and completing several identical questionnaires, including the Depression Anxiety and Stress Scales (DASS-21)[8] and the Delaying Gratification Inventory (DGI).[9] Additionally, in both cases the TD task was done on a laptop with an experimenter present. Data were collected between May 2014 and September 2015.

Temporal Discounting Task

TD was assessed using a computerized hypothetical monetary choice task, modeled on an established paradigm.[5] On each of 80 trials, participants had an unrestricted amount of time to indicate whether they would prefer to receive a smaller amount of money immediately (smaller-sooner reward) or a larger amount after 3 months (larger-later reward). Two types of decision framing were employed: "Accelerate" (larger-later reward remained at £100, smaller-sooner reward increased from £20 to £98 in £2 increments) and "Delay" (smaller-sooner reward remained at £50, larger-later reward increased from £52 to £130 in £2 increments) (40 trials for each). The trials were pseudo-randomly interleaved, so that the two decision frames were intermixed.

TD was quantified by determining participants' discount factor (DF)—the magnitude of reduction in the present value of a future reward—for each choice set using a two-step procedure[5] (see Appendix B). Global DF was calculated as the mean of the two DFs, and was used as the primary outcome variable in this study. The value obtained can range from 0 to 1, with smaller numbers indicating greater TD (i.e., a greater tendency to choose the smaller-sooner reward).

Delaying Gratification Inventory

Self-reported ability to delay gratification was measured with the DGI, which requires respondents to rate the extent to which they agree with 35 statements on a 5-point Likert scale. Scores are generated for five domains of delay behavior (Food, Physical Pleasures, Social Interactions, Money, and Achievement) and a total score (Global DGI score) is calculated. This was used as the outcome variable here. Higher values indicate a greater capacity to delay gratification.

Results

Statistical analyses were performed using SPSS® (tests were two-tailed, $\alpha = 0.05$). Key sample characteristics and raw intertemporal choice data are provided in **Table 1**. TD data were positively skewed, therefore square-root transformations were applied and transformed values were used in all subsequent analyses. Global DFs and Global DGI scores were correlated in the sample as a whole [$r = .33$, $p = .002$] (i.e., the higher the rate of TD, the lower the ability to delay gratification).

A one-way multivariate ANOVA showed that individuals with BN had lower Global DFs (indicating an increased rate of TD) [$F(1, 90) = 5.72$, $p = .019$] and Global DGI scores (indicating a reduced capacity to delay gratification) [$F(1, 90) = 41.65$, $p < .001$] than HC. To examine whether these group differences persisted after controlling for other possible determinants, age, gender, BMI, and DASS-21 depression, anxiety, and stress scores were entered into the model as covariates. This revealed a significant effect of group on Global DF [$F(1, 84) = 5.52$, $p = .021$] but not Global DGI score [$F(1, 84) = 2.24$, $p = .138$], due to the inclusion of DASS-21 stress scores [$F(1, 84) = 5.25$, $p = .024$]. An exploratory mixed ANOVA revealed no significant main effect of framing (Accelerate vs. Delay) or framing × group interaction on DFs [both $p \geq .654$].

Bivariate correlations were used to explore the relationships between Global DFs, Global DGI scores, clinical outcomes (DASS-21 and EDE-Q scores, illness duration, and frequency of binge-

TABLE 1. Sample characteristics and raw intertemporal choice data

	HC ($n = 53$)		BN ($n = 39$)		
	M [n]	SD [%]	M [n]	SD [%]	p
Age	25.55	7.33	25.85	6.62	.442[a]
Gender	–	–	–	–	.083[b]
Female	[44]	[83.02]	[37]	[94.87]	–
Male	[9]	[16.98]	[2]	[5.13]	–
BMI[c]	21.71	2.17	21.65	3.20	.420[a]
DASS-21 depression	2.68	2.96	20.62	10.39	<.000[a]
DASS-21 anxiety	2.57	3.60	15.23	11.65	<.000[a]
DASS-21 stress	6.64	5.24	21.97	10.19	<.000[d]
EDE-Q global	–	–	4.21	1.06	–
Illness duration (months)	–	–	110.87	95.62	–
Binge-eating frequency[e]	–	–	22.23	31.66	–
Vomiting frequency[e]	–	–	50.87	169.5	–
Laxative use frequency[e]	–	–	4.69	17.28	–
Excessive exercise frequency[e]	–	–	7.21	9.99	–
DF Accelerate	0.45	0.35	0.32	0.34	.046[a]
DF Delay	0.42	0.31	0.27	0.04	.012[a]
DF Global	0.44	0.31	0.30	0.29	.020[a]
DGI global	140.79	12.86	121.85	15.24	<.000[d]

HC, healthy controls; BN, bulimia nervosa; DF, discount factor (from temporal discounting task); DGI, Delaying Gratification Inventory; M, mean; SD, standard deviation; BMI, body mass index.
[a]Mann–Whitney U test.
[b]Pearson chi-squared test.
[c]Weight(kg)/(height(m))^2.
[d]Independent samples t test.
[e]Number of times in the previous 28 days.

eating, vomiting, laxative use, and excessive exercise), and BMI. Pearson's r and Spearman's rho correlation coefficients were employed. In the BN group, Global DFs were not significantly related to any clinical variables [all $p > .109$], and Global DGI scores were also not significantly correlated with any clinical variables [all $p \geq .278$] except for DASS-21 depression [$r = -0.34$, $p = .036$] and stress [$r = -0.39$, $p = .013$] scores. Neither Global DFs nor Global DGI scores were associated with BMI when the BN and HC groups were considered separately or together [all $p \geq .233$].

Discussion

This is the first study to assess intertemporal choice behavior in BN. Individuals with BN displayed steeper rates of TD (i.e., an increased preference for smaller-sooner rewards) and a reduced self-reported capacity to delay gratification compared to HC. This is consistent with observations of disadvantageous monetary decision-making in BN[3] and with TD findings in BED,[4] but contrasts with the lower rates of TD reported in AN (which reflect an increased preference for larger-later rewards).[5]

Group differences in TD remained significant after controlling for variables reported to influence discounting rates (age, gender, BMI, depression, anxiety, and stress). TD did not correlate with illness duration, symptom severity, general psychopathology, or BMI among individuals with BN, suggesting that elevated TD reflects a stable neurocognitive feature of BN; however, as our study only included acutely ill individuals, we cannot determine whether TD is a trait- or state-based marker of illness. Interestingly, a recent study reported that reduced TD in AN normalized after weight restoration[10]; thus, studies should explore whether increased TD in BN persists after recovery. In contrast to TD rates, group differences in DGI scores disappeared after controlling for stress, and a decreased self-reported capacity to delay reward was associated with greater stress and depression in the BN group. Stress may therefore influence the perception of one's tendencies to delay gratification, but not the behavior itself. We did not replicate the finding that people discount future rewards more when they are asked to delay consumption than when they are offered the chance to accelerate consumption,[5,11] which may be due to differences in the TD task administered.

A reduced capacity to delay reward may underpin some of the core symptoms of BN. For example, greater TD is proposed to reflect choice impulsivity and poor reward-related inhibitory control,[12] and these neurocognitive difficulties are implicated in binge-eating and compensatory behaviors. Furthermore, binge-eating can be regarded as a manifestation of the tendency to act in pursuit of immediate pleasure-driven desires, as people with BN have heightened reward sensitivity

to food cues[13] and report that binge-eating relieves negative affect.[14] Altered intertemporal choice behavior could therefore be a relevant target for intervention in this patient group.

Excessive TD is not exclusive to BN and BED: it relates to a broader set of psychiatric conditions, including addictions and schizophrenia, and to a number of behavioral maladies, such as unsafe sex and poor health practices.[15] It has therefore been proposed to function as a trans-disease process, potentially underscored by a neurobiological imbalance between the "impulsive" and "executive" decision systems, which are embodied in parts of the limbic/paralimbic brain regions and prefrontal cortices, respectively.[15] In this view, effective interventions will be those that restore regulatory balance to these competing systems.[16] Indeed, we recently found that direct manipulation of the executive system with transcranial magnetic stimulation concurrently altered TD and improved symptoms in AN.[17]

This study has some limitations. First, most participants were women, which may have introduced a gender bias[18]; however, the male-to-female ratio did not differ between groups and a predominantly female sample reflects the higher prevalence of BN in women than in men. Second, we were unable to explore between-group differences in income, education, or IQ, which may influence the subjective evaluation of monetary rewards.[19,20] Finally, although the paradigm included more trials than most TD tasks, our findings are restricted to choices between immediate rewards and those delayed by three months: future studies should confirm the results using multiple time-points, permitting hyperbolic modeling of discounting.

Appendix A

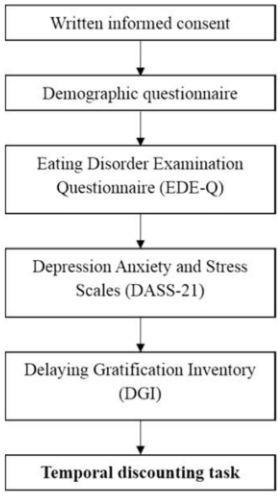
Further Description of the Two Larger Studies

The two studies had unrelated aims: Study 1 was a crossover randomized controlled trial assessing the effects of transcranial direct current stimulation (tDCS) in bulimia nervosa, and Study 2 explored the impact of acute food restriction and distractor relevance on inhibitory control in healthy controls. Whereas these studies assessed within-subject differences in temporal discounting due to tDCS treatment and acute fasting, respectively, the present research combined their baseline temporal discounting and delaying gratification data to evaluate between-group differences in intertemporal choice behavior.

The flow charts below show the measures completed prior to the temporal discounting task in each study. Full procedural details are available on request.

Study 1: Transcranial direct current stimulation improves symptoms, mood, and self-regulatory control in bulimia nervosa: A proof-of-principle clinical trial

Study 2: The impact of acute food restriction and distractor relevance on inhibitory control in healthy adults



Appendix B

Two-Step Procedure for Quantification of Discounting Rate

First, the "indifference point" was established. This is the amount of money that the participant judged as equivalent to the fixed reward—i.e., the value of the variable reward when the participant switched from larger-later to smaller-sooner in the Accelerate set and from smaller-sooner to larger-later in the Delay set.[5] Second, a mathematical formula was fitted to the indifference point: $\delta = (x_1/x_2)^{(1/(t2\ -\ t1))}$, where x_1 is the smaller-sooner reward, x_2 is the larger-later reward, and $t_2 - t_1$ is the delay to reward presentation (in years), which in this case was 0.25.[5,11] This procedure is a sensitive measure of temporal discounting that is independent of hyperbolic modeling and area under the curve analyses.[5,11]

REFERENCES

1. Guillaume S, Sang CNT, Jaussent I, Raingeard I, Bringer J, Jollant F, et al. Is decision making really impaired in eating disorders? Neuropsychology 2010;24:808–812.
2. Van den Eynde F, Guillaume S, Broadbent H, Stahl D, Campbell I, Schmidt U, et al. Neurocognition in bulimic eating disorders: A systematic review. Acta Psychiatr Scand 2011;124:120–140.
3. Guillaume S, Gorwood P, Jollant F, Van den Eynde F, Courtet P, Richard-Devantoy S. Impaired decision-making in symptomatic anorexia and bulimia nervosa patients: A meta-analysis. Psychol Med 2015;45:3377–3391.
4. Mole TB, Irvine MA, Worbe Y, Collins P, Mitchell SP, Bolton S, et al. Impulsivity in disorders of food and drug misuse. Psychol Med 2015;45:771–782.
5. Steinglass JE, Figner B, Berkowitz S, Simpson HB, Weber EU, Walsh BT. Increased capacity to delay reward in anorexia nervosa. J Int Neuropsychol Soc 2012;18:773–780.
6. Stice E, Telch CF, Rizvi SL. Development and validation of the Eating Disorder Diagnostic Scale: A brief self-report measure of anorexia, bulimia, and binge-eating disorder. Psychol Assess 2000;12:123–131.
7. First MB, Spitzer RL, Gibbon M, Williams JB. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-Patient Edition (SCID-I/NP). New York: Biometrics Research, 2002.
8. Lovibond SH, Lovibond PF. Manual for the Depression Anxiety Stress Scales, 2nd ed. Sydney: Psychology Foundation, 1995.
9. Hoerger M, Quirk SW, Weed NC. Development and validation of the Delaying Gratification Inventory. Psychol Assess 2011;23:725–738.
10. Decker JH, Figner B, Steinglass JE. On weight and waiting: Delay discounting in anorexia nervosa pretreatment and posttreatment. Biol Psychiatry 2015;78:606–614.
11. Weber EU, Johnson EJ, Milch KF, Chang H, Brodscholl JC, Goldstein DG. Asymmetric discounting in intertemporal choice: A query-theory account. Psychol Sci 2007;18:516–523.
12. Bari A, Robbins TW. Inhibition and impulsivity: Behavioral and neural basis of response control. Prog Neurobiol 2013;108:44–79.
13. Brooks SJ, O'Daly OG, Uher R, Friederich HC, Giampietro V, Brammer M, et al. Differential neural responses to food images in women with bulimia versus anorexia nervosa. PLoS One 2011;6:e22259.
14. De Young KP, Zander M, Anderson DA. Beliefs about the emotional consequences of eating and binge eating frequency. Eat Behav 2014;15:31–36.
15. Bickel WK, Jarmolowicz DP, Mueller ET, Koffarnus MN, Gatchalian KM. Excessive discounting of delayed reinforcers as a trans-disease process contributing to addiction and other disease-related vulnerabilities: Emerging evidence. Pharmacol Ther 2012;134:287–297.
16. Koffarnus MN, Jarmolowicz DP, Mueller ET, Bickel WK. Changing delay discounting in the light of the competing neurobehavioral decision systems theory: A review. J Exp Anal Behav 2013;99:32–57.
17. McClelland J, Kekic M, Bozhilova N, Nestler S, Dew T, Van den Eynde F, et al. A randomised controlled trial of neuronavigated repetitive transcranial magnetic stimulation (rTMS) in anorexia nervosa. PLoS One 2016;11:e0148606.
18. Weller RE, Cook EW, III, Avsar KB, Cox JE. Obese women show greater delay discounting than healthy-weight women. Appetite 2008;51:563–569.
19. Green L, Myerson J, Lichtman D, Rosen S, Fry A. Temporal discounting in choice between delayed rewards: The role of age and income. Psychol Aging 1996;11:79.
20. de Wit H, Flory JD, Acheson A, McCloskey M, Manuck SB. IQ and nonplanning impulsivity are independently associated with delay discounting in middle-aged adults. Pers Individ Dif 2007;42:111–121.

APPENDIX B: ETHICAL APPROVAL

Appendix B.1 Ethical approval for study of tDCS in healthy individuals with frequent food cravings

Maria Kekic
50 Azalea Walk
Pinner
Middlesex HA5 2EH

27 March 2013

Dear Maria

PNM/12/13-112 An investigation into the effects of transcranial direct current stimulation (tDCS) on food cravings and self-regulation in healthy women.

Review Outcome: Full Approval

Thank you for submitting an application to the **PNM RESC** which was reviewed on **19 March 2013**. I am pleased to inform you that these meet the requirements of the PNM RESC and therefore that full approval is now granted with the following provisos:

1. Section 2.8: Please complete this section. Please email your response to Rebecca Cowper: Rebecca.cowper@kcl.ac.uk, quoting your reference number on all correspondence.
2. Consent Form: Please use tick boxes for all of the statements, permitting participants to consent to each clause.
3. Demographic Information: Please use standard ethnicity classifications, from the 2011 Census. (See http://www.ons.gov.uk/ons/guide-method/measuring-equality/equality/ethnic-nat-identity-religion/ethnic-group/index.html#8)

Note that you should submit a response to the above provisos where specified; it is a condition of the approval granted by the PNM RESC that the provisos are carried out prior to the study commencing. If the provisos are not adhered to, the approval granted by the PNM RESC would no longer be valid. Should you have any queries on this please do not hesitate to contact the Research Ethics Office.

Please ensure that you follow all relevant guidance as laid out in the King's College London Guidelines on Good Practice in Academic Research (http://www.kcl.ac.uk/college/policyzone/index.php?id=247).

For your information ethical approval is granted until **19 March 2014**. If you need approval beyond this point you will need to apply for an extension to approval at least two weeks prior to this explaining why the extension is needed, (please note however that a full re-application will not be necessary unless the protocol has changed). You should also note that if your approval is for one year, you will not be sent a reminder when it is due to lapse.

Ethical approval is required to cover the duration of the research study, up to the conclusion of the research. The conclusion of the research is defined as the final date or event detailed in the

study description section of your approved application form (usually the end of data collection when all work with human participants will have been completed), not the completion of data analysis or publication of the results. For projects that only involve the further analysis of pre-existing data, approval must cover any period during which the researcher will be accessing or evaluating individual sensitive and/or un-anonymised records. Note that after the point at which ethical approval for your study is no longer required due to the study being complete (as per the above definitions), you will still need to ensure all research data/records management and storage procedures agreed to as part of your application are adhered to and carried out accordingly.

If you do not start the project within three months of this letter please contact the Research Ethics Office.

Should you wish to make a modification to the project or request an extension to approval you will need approval for this and should follow the guidance relating to modifying approved applications: http://www.kcl.ac.uk/innovation/research/support/ethics/applications/modifications.aspx
The circumstances where modification requests are required include the addition/removal of participant groups, additions/removal/changes to research methods, asking for additional data from participants, extensions to the ethical approval period. Any proposed modifications should only be carried out once full approval for the modification request has been granted.

Any unforeseen ethical problems arising during the course of the project should be reported to the approving committee/panel. In the event of an untoward event or an adverse reaction a full report must be made to the Chair of the approving committee/review panel within one week of the incident.

Please would you also note that we may, for the purposes of audit, contact you from time to time to ascertain the status of your research.

If you have any query about any aspect of this ethical approval, please contact your panel/committee administrator in the first instance (http://www.kcl.ac.uk/innovation/research/support/ethics/contact.aspx). We wish you every success with this work.

With best wishes

Yours sincerely

Rebecca Cowper
Research Support Assistant
For and on behalf of
Mrs Joyce Epstein, Vice-Chair
Psychiatry, Nursing and Midwifery Research Ethics Subcommittee (PNM RESC)

Cc: Professor Ulrike Schmidt

Appendix B.2 Ethical approval for study of tDCS in patients with bulimia nervosa (BN)

NHS
Health Research Authority

NRES Committee London - City Road & Hampstead
Bristol Research Ethics Committee Centre
Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 342 1339

10 February 2014

Miss Maria Kekic
PhD student
Institute of Psychiatry, P059
16 De Crespigny Park
London
SE5 8AF

Dear Miss Kekic

Study title:	**An experimental sham-controlled crossover study of prefrontal cortex transcranial direct current stimulation (tDCS) in patients with anorexia nervosa and bulimia nervosa**
REC reference:	**14/LO/0025**
IRAS project ID:	**141428**

Thank you for your letter of 30 January 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager, Tina Cavaliere at nrescommittee.london-cityroadandhampstead@nhs.net.

Confirmation of ethical opinion

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

I am pleased to confirm that the favourable opinion applies to the following research site(s), subject to site management permission being obtained prior to the start of the study at the site (see under 'Conditions of the favourable opinion below').

Research Site	Principal Investigator / Local Collaborator
Institute of Psychiatry	Miss Maria Kekic

Confirmation of approval for other sites listed in the application will be issued as soon as the SSA(s) has been reviewed by the Committee.

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

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

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	1 - Poster	11 November 2013
Advertisement	1 KCL Recruitment	19 November 2013
Covering Letter		29 November 2013
Evidence of insurance or indemnity		26 November 2013
GP/Consultant Information Sheets	1	18 November 2013
Investigator CV		25 November 2013
Other: CV for Supervisor		25 November 2013
Other: SSI Form		29 November 2013
Other: E-mail clarification re patient involvement group		30 January 2014
Participant Consent Form	2	11 November 2013
Participant Information Sheet: AN	2	28 January 2014
Participant Information Sheet: BN	2	28 January 2014
Protocol	2	11 November 2013
Questionnaire: EDE-Q		
Questionnaire: EDDS		
Questionnaire: SCID		
Questionnaire: DASS-21		
Questionnaire: Demographic Information	1	25 November 2013
Questionnaire: Inclusion/Exclusion criteria	1	25 November 2013
Questionnaire: Food Challenge Task	1	25 November 2013
Questionnaire: Visual Analogue scales	1	26 November 2013
Questionnaire: Tolerance questionnaire	1	26 November 2013
Questionnaire: Acceptability questionnaire	1	26 November 2013
Questionnaire: Test of Blinding	1	26 November 2013
REC application		03 December 2013

Response to Request for Further Information		30 January 2014
Summary/Synopsis	2	11 November 2013

Statement of compliance

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

After ethical review

Reporting requirements

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

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

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

Feedback

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

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

14/LO/0025	**Please quote this number on all correspondence**

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

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

Yours sincerely

Dr David Slovick
Chair

Email:nrescommittee.london-cityroadandhampstead@nhs.net

Appendix B.3 Ethical approval for study of temporal discounting in healthy individuals[16]

Research Policy & Ethics

5.11 Franklin Wilkins Building
(Waterloo Bridge Wing)
Stamford Street
London SE1 9NH
Tel 020 7848/4077/4070/3758
Email rec@kcl.ac.uk
www.kcl.ac.uk/research/ethics

KING'S College LONDON

Savani Bartholdy
47 Cedar House
Lensbury Avenue
London SW6 2GU

29 May 2014

Dear Savani,

PNM/13/14-147 Exploring the effects of motivational stimuli on proactive and reactive response inhibition.

Review Outcome: Full Approval

Thank you for sending in the amendments/clarifications requested to the above project. I am pleased to inform you that these meet the requirements of the PNM RESC and therefore that full approval is now granted.

Provisos
Your approval is based on the following provisos being met:

1. Sections 2.2 and 2.3: Please note that ethical approval for PhD studies is normally granted for a period of three years.
2. Section 6.1: The Committee approves the recruitment of up to 40 participants.
3. Section 6.3: The Committee assumes that it will be incumbent on those interested in taking part to contact you.
4. Section 7.1: The Committee recommends that participants are allowed at least 24 hours to consider whether to take part after reading the Information Sheet.
5. Section 7.2: Specify a date as the deadline for withdrawal of participant data. This should appear on the Information Sheet.
6. Section 8.2: The Committee recommends that all participants are reimbursed even if they withdraw after the first session.
7. Application Form B – G1:
    I. The Committee assumes that your answer to the question as to whether you are collecting 'new relevant material' should be 'yes'.
    II. Please insert the date of your last HTA training.
8. Information Sheet:
    III. Provide more information about the questions posed by the questionnaires.
    IV. Replace 'King's College London (KCL) College Research Ethics Committee (CREC)' with 'Psychiatry, Nursing and Midwifery (PNM) Research Ethics Subcommittee (RESC) at King's College London'.

V. Delete the paragraph entitled 'What if there is a problem?' Replace the current sentence starting "'If this study has harmed you..." at the end of part two of the Information sheet with the following: 'If this study has harmed you in any way or if you wish to make a complaint about the conduct of the study you can contact King's College London using the details below for further advice and information:' The contact details for your supervisor should follow.

You are not required to provide evidence to the Committee that these provisos have been met, but your ethical approval is only valid if these changes are made. You must not commence your research until these provisos have been met.

Please ensure that you follow all relevant guidance as laid out in the King's College London Guidelines on Good Practice in Academic Research (http://www.kcl.ac.uk/college/policyzone/index.php?id=247).

For your information ethical approval is granted until 29 May 2017. If you need approval beyond this point you will need to apply for an extension to approval at least two weeks prior to this explaining why the extension is needed, (please note however that a full re-application will not be necessary unless the protocol has changed). You should also note that if your approval is for one year, you will not be sent a reminder when it is due to lapse.

Ethical approval is required to cover the duration of the research study, up to the conclusion of the research. The conclusion of the research is defined as the final date or event detailed in the study description section of your approved application form (usually the end of data collection when all work with human participants will have been completed), not the completion of data analysis or publication of the results.
For projects that only involve the further analysis of pre-existing data, approval must cover any period during which the researcher will be accessing or evaluating individual sensitive and/or un-anonymised records.
Note that after the point at which ethical approval for your study is no longer required due to the study being complete (as per the above definitions), you will still need to ensure all research data/records management and storage procedures agreed to as part of your application are adhered to and carried out accordingly.

If you do not start the project within three months of this letter please contact the Research Ethics Office.

Should you wish to make a modification to the project or request an extension to approval you will need approval for this and should follow the guidance relating to modifying approved applications: http://www.kcl.ac.uk/innovation/research/support/ethics/applications/modifications.aspx

Please would you also note that we may, for the purposes of audit, contact you from time to time to ascertain the status of your research.

If you have any query about any aspect of this ethical approval, please contact your panel/committee administrator in the first instance (http://www.kcl.ac.uk/innovation/research/support/ethics/contact.aspx) We wish you every success with this work.

[16] Data from this trial was used to conduct the cross-sectional study that forms chapter 4.

Yours sincerely,

James Patterson - Senior Research Ethics Officer
For and on behalf of
Professor Gareth Barker, Chairman
Psychiatry, Nursing and Midwifery Research Ethics Subcommittee (PNM RESC)

Cc: Ulrike Schmidt

APPENDIX C: RECRUITMENT DOCUMENTS

Appendix C.1 Recruitment documents for study of tDCS in healthy individuals with frequent food cravings

Appendix C.1.1 *Poster*

Appendix C.1.2 *King's College London (KCL) recruitment email*

Transcranial direct current stimulation (tDCS) in food cravings and decision making – advertisement

Advertisement for use for recruitment of volunteers for study ref: PNM/12/13-112, approved by the Psychiatry, Nursing and Midwifery Research Ethics Subcommittee (PNM RESC). This project contributes to the College's role in conducting research, and teaching research methods. You are under no obligation to reply to this email, however if you choose to, participation in this research is voluntary and you may withdraw at anytime.

Research shows that the frontal areas of the brain play a role in the control of eating, and that variation in activity in these areas might explain why some people get food cravings and others do not. The same areas might also be involved in decision making processes. This study aims to find out whether a single session of tDCS (a technique used to stimulate specific areas of the brain) has any short-term effects on food cravings and decision making in healthy women.

To take part you must be a female aged between 18 and 60 who has frequent food cravings (your eligibility will be confirmed over a 20 minute telephone call). If you choose to participate you will be required to attend two sessions (48 hours apart) at the Institute of Psychiatry, lasting 1.5-2 hours each. The sessions will involve completing a series of questionnaires, a neuropsychological task (brain puzzle), and a food task. You will also receive a 20-minute tDCS session and have saliva samples collected to measure cortisol levels (a stress hormone). You will be reimbursed £30 for your time plus travel expenses (up to £5).

If you are interested in taking part or would like further information please email maria.kekic@kcl.ac.uk or call 07814798727. Full details of the study will be available on the participant information sheet that will be sent to you upon response to this advertisement. Pease note that contacting us for further information does not mean you are obliged to take part in the study.

Thank you for your time, I look forward to hearing from you soon.
Maria Kekic

Appendix C.2 Recruitment documents for study of tDCS in patients with BN

Appendix C.2.1 *Poster/flyer*

Appendix C.2.2 *Text for KCL and Experimatch recruitment webpage advertisements*

TREAT - Transcranial direct current stimulation (tDCS) in eating disorders

We are investigating the effects of a non-invasive brain stimulation technique called transcranial direct current stimulation (tDCS) on eating disorder symptoms in people with bulimia nervosa.

Advertisement for use for recruitment of volunteers for study ref: 14/LO/0025, approved by the City Road and Hampstead Ethics Committee. This project contributes to the college's role in conducting research, and teaching research methods. You are under no obligation to reply to this email, however if you choose to, participation in this research is voluntary and you may withdraw at anytime.

Psychological therapies are often ineffective for people with bulimia nervosa (BN); therefore there is an ongoing need for the development of new treatments. Research shows that the frontal areas of the brain play a role in the development and maintenance of eating disorders, including BN. Stimulating these brain areas to alter 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 called transcranial direct current stimulation (tDCS). This involves the delivery of a low electrical current via small electrodes placed on the scalp. This procedure is widely used in research and is being applied in clinical settings.

This study aims to investigate the short-term effects of a single session of tDCS in individuals who suffer from BN. In particular, we are interested in its effects on thought processes and emotions relating to food, eating, weight, and body shape. In the long term, this may help us to develop improved treatments for BN.

To take part you must be a male or female aged between 18 and 70 who has a current diagnosis of BN or a related disorder (your eligibility will be confirmed over a 20-minute telephone call). If you choose to participate you will be required to attend three sessions at the Institute of Psychiatry, lasting approximately 1.5 hours each. The sessions will involve completing a series of questionnaires, a neuropsychological task (brain puzzle), and a food task (you will not be asked to eat any food). You will also receive a 20-minute tDCS session. You will be reimbursed £50 for your time.

If you are interested in taking part or would like further information please email maria.kekic@kcl.ac.uk or call 02078480183. Full details of the study will be available on the participant information sheet that will be sent to you upon response to this advertisement. Please note that contacting us for further information does not mean you are obliged to take part in the study.

Thank you for your time, I look forward to hearing from you soon.
Maria Kekic

Appendix C.2.3 *Text for Beat recruitment webpage advertisement*

Transcranial direct current stimulation (tDCS) in bulimia nervosa

Psychological therapies are often ineffective for people with bulimia nervosa (BN); therefore there is an ongoing need for the development of new treatments. Research shows that the frontal areas of the brain play a role in the development and maintenance of eating disorders, including BN. Stimulating these brain areas to alter 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 called transcranial direct current stimulation (tDCS). This involves the delivery of a low electrical current via small electrodes placed on the scalp. This procedure is safe, painless, and is widely used in research.

Our aims

This study aims to investigate the short-term effects of a single session of tDCS in individuals who suffer from BN. In particular, we are interested in its effects on thought processes and emotions relating to food, eating, weight, and body shape. In the long term, this may help us to develop improved treatments for BN.

What's involved?

If you choose to participate you will be required to attend three sessions at the Institute of Psychiatry (Denmark Hill), lasting 1.5-2 hours each. The sessions will involve completing a series of questionnaires, a neuropsychological task (brain puzzle), and a food task (you will not be asked to eat any food). You will also receive a 20-minute session of tDCS. After the third session you will be reimbursed £50 for your time and effort.

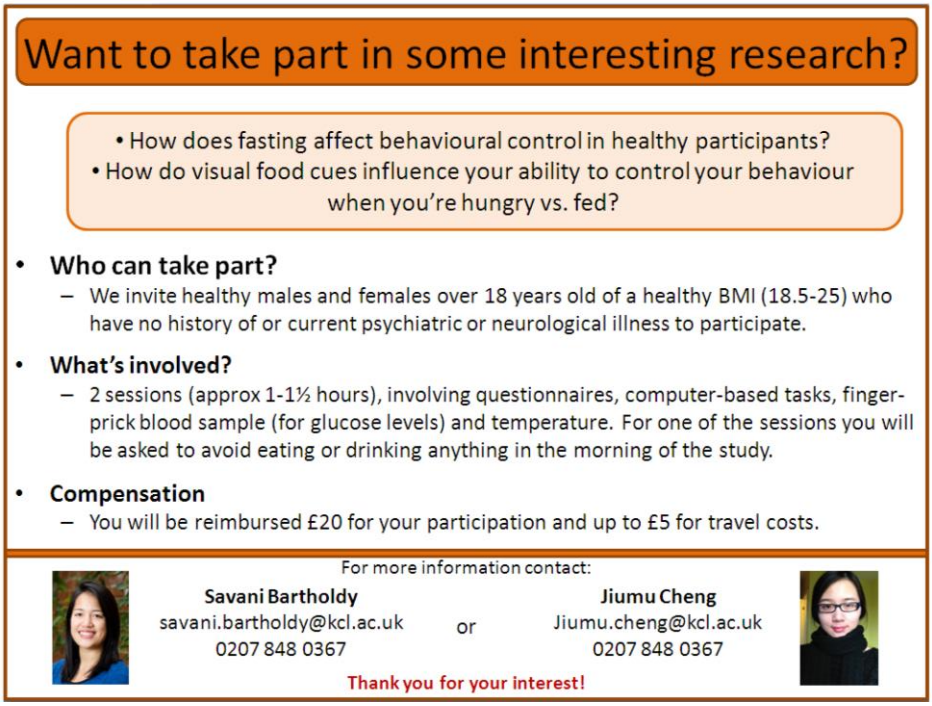
Can I take part?

We are looking for males and females aged between 18 and 70 who have a current diagnosis of BN or a related disorder (your eligibility will be confirmed over a 20-minute telephone call). Taking part in this study will not influence the timing of any treatment you are currently receiving for your eating disorder.

If you are interested in taking part or would like further information please contact Maria Kekic (maria.kekic@kcl.ac.uk, 02078480183). Please note that contacting us for further information does not mean you are obliged to take part in the study. Participation in this research is voluntary and if you decide to take part you may withdraw at any time without giving a reason.

Appendix C.3 Recruitment documents for study of temporal discounting in healthy individuals

Appendix C.3.1 *Poster*



Appendix C.2.2 *Text for KCL recruitment webpage advertisement*

Exploring the effects of motivational stimuli on response inhibition - advertisement.

Synopsis:
We are interested in seeing how fasting and food cues affect self control in healthy individuals to get an idea of how this may be involved in the atypical behavioural control seen in eating disorders.

Advertisement for use in the recruitment of volunteers for study ref: PNM/13/14-147 approved by the King's College London (KCL) College Research Ethics Committee (CREC). This project contributes to the College's role in conducting research, and teaching research methods. You are under no obligation to reply to this email, however if you choose to, participation in this research is voluntary and you may withdraw at any time.

Eating disorders (ED) are associated with atypical control over one's behaviour. However, it is not yet clear whether all types of behavioural control is different in EDs compared to healthy individuals. Our team are trying to build a comprehensive picture of what types of behavioural control is atypical across the ED spectrum. To do this, we first need to pilot some new behavioural paradigms in healthy people without eating disorders (or any other major psychiatric disorder). In addition, we are interested in seeing how fasting affects your self control to get an idea of how this may be involved in the atypical behavioural

control seen in ED patients. We are also interested in seeing how food cues affect your ability to inhibit your responses, and how this effect differs in the fed and fasted state.

We are looking for volunteers to participate in our study. To take part, you must be a male or female over 18 years old with no history of or current psychiatric or neurological illness. If you choose to participate, you will be asked to meet with the researcher on **two separate occasions**. Each session will last approximately **1 to 1.5 hours**. On both sessions, you will be asked to complete a series of questionnaires, followed by several computer-based tasks. Your weight and height will be measured, and you will have a small blood sample taken by a finger prick. This sample is to monitor your blood glucose. On one of the sessions, you will be asked to avoid eating or drinking anything in the morning of the study. This will be your 'fasted' session. Both sessions will take place in the morning before noon, so that in your fasted session you will only be asked to skip breakfast.

Appointments take place at the Institute of Psychiatry at 103 Denmark Hill.We are offering **£20** as a token of thanks (£10 per session), and up to **£5** travel compensation per visit upon proof of receipt.

If you are interested in participating, or would like further information, please send an email to **savani.bartholdy@kcl.ac.uk** with your contact details or call 0207 848 0367. Full details will be available on the participant information sheet that you will be sent if you respond to this email. Please note that contacting us does not mean you have to take part in the study.

Thank you for taking the time to read this message. I look forward to hearing from you.

Kind regards,
Savani Bartholdy

APPENDIX D: PARTICIPANT INFORMATION SHEETS

Appendix D.1 Information sheet for study of tDCS in healthy individuals with frequent food cravings

INFORMATION SHEET FOR PARTICIPANTS

REC Reference Number: PNM/12/13-112

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET

An investigation into the effects of transcranial direct current stimulation (tDCS) on food cravings and self-regulation in healthy women

We would like to invite you to participate in this postgraduate research project. You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

Aims of the research and possible benefits

Research shows that the frontal areas of the brain play a role in the control of eating, and that variation in activity in these areas might explain why some people get food cravings and others do not. The same areas might also be involved in decision making processes. Stimulating these areas to alter their functioning is therefore believed to have the potential to reduce food cravings and to affect decision making. A technique that is capable of stimulating specific brain areas is called transcranial direct current stimulation (tDCS). This involves the delivery of low currents via small electrodes placed on the scalp. This procedure is widely used in research and is being applied in clinical settings. This study, funded by King's College London, aims to find out whether a single session of tDCS has any short-term effects on food cravings and decision making in healthy women. In the long term, this may help us to develop strategies to help people control their food cravings.

Who can participate?

You are invited to participate if you are a female aged between 18 and 60 who experiences frequent food cravings. We will be recruiting 20 participants in total.

Unfortunately you cannot participate if you:
- Take anti-convulsive medication
- Take antipsychotic medication
- Are on a dose of any psychotropic medication that has not been stable for at least 14 days prior to participation
- Are pregnant
- Smoke more than 10 cigarettes per day
- Have a current major psychiatric disorder needing treatment
- Have a food allergy (including to chocolate, biscuits, potato crisps, or nuts, or to any of the ingredients these foods contain e.g. milk)
- Have had a seizure
- Have someone in your family who has epilepsy
- Have had a stroke

- Have any metal in your head (outside the mouth)
- Suffer from severe or frequent headaches
- Have had a serious head injury or any brain-related condition
- Have any implanted devices (e.g. cardiac pacemakers, medical pumps)

What will happen if you agree to take part?
You do not have to take part in this experiment; it is your choice. If you decide you want to participate you will firstly be asked to engage in a telephone conversation with the experimenter (lasting approximately 20 minutes) to confirm that you are eligible to take part. If you are, you will be invited to the Institute of Psychiatry on a day that is convenient for both you and the researchers, in either the morning or the afternoon. You will be asked to return two days later at the same time. Upon arrival to your first visit you will be asked to sign a consent form to confirm that you want to participate.

Each visit will take 1.5-2 hours and will involve completing a series of questionnaires (assessing mood and eating habits), a neuropsychological task (brain puzzle), and a food task for which you will be asked to rate different foods. You will be given the opportunity to eat some of these foods if you wish to. You will also receive a 20-minute tDCS session, and have saliva samples collected to measure cortisol levels (a stress hormone). During the tDCS session you will sit on a comfortable chair and wear a plastic headband to keep the electrodes in place. The researcher will turn the machine on which will deliver the currents. There is no need for any special preparation before the visits.

If you decide to take part you will be free to withdraw from the study at any time without giving a reason. You may also withdraw any data or information you have already provided up until it is transcribed for use in the final report (30/06/13).

Are there any risks involved?
There are no risks involved in taking part in this study; however, you may find the procedure slightly uncomfortable. This is because a number of sensations can occur beneath the electrodes during stimulation including tingling, pain, itching, and burning. Not everyone feels these sensations or finds them uncomfortable, but if you do remember you are free to stop the study at any point without giving an explanation.

Will you benefit from taking part?
This study is not intended to help any individual participant, but the information we get may help us to develop strategies to help people control their food cravings. Upon completion of your second visit you will be reimbursed £30 (plus travel expenses up to £5) for your time and effort.

What will happen to the data collected?
Your personal information and the data we collect from you will remain confidential at all times. It will also remain anonymous to everyone apart from the primary researchers. 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 written feedback of the study's findings you can contact the researcher (contact details below) for a summary. The results will be included in an examined postgraduate report, presented as part of a postgraduate presentation, and sent to a medical journal for publication. Your participation in the study will not be disclosed.

What to do if you have more questions
If you have any questions or require more information about this study, please contact the researcher using the following contact details:

Maria Kekic (maria.kekic@kcl.ac.uk)
Department of Psychological Medicine

Eating Disorders
103 Denmark Hill (1st floor)
SE5 8AZ

If this study has harmed you in any way you can contact King's College London using the following details for further advice and information:

Ulrike Schmidt (ulrike.schmidt@kcl.ac.uk)
Department of Psychological Medicine
Eating Disorders
103 Denmark Hill (1st floor)
SE5 8AZ

Appendix D.2 Information sheet for study of tDCS in patients with BN

PARTICIPANT INFORMATION SHEET

KING'S College LONDON

An investigation into the effects of transcranial direct current stimulation (tDCS) in bulimia nervosa

Research Ethics Committee reference number: 14/LO/0025

We would like to invite you to participate in this postgraduate research project. You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study. Please ask us if there is anything that is not clear or if you would like more information.

PART ONE

What is the purpose of the study?

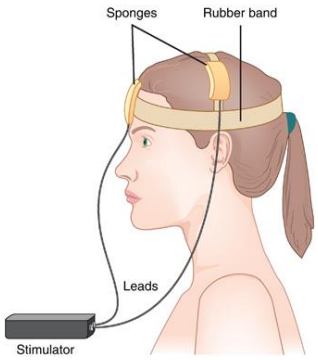
Psychological therapies are often ineffective for people with bulimia nervosa (BN); therefore there is an ongoing need for the development of new treatments. Research shows that the frontal areas of the brain play a role in the development and maintenance of eating disorders, including BN. Stimulating these brain areas to alter 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 called transcranial direct current stimulation (tDCS). This involves the delivery of a low electrical current via small electrodes placed on the scalp. This procedure is widely used in research and is being applied in clinical settings.

This study aims to investigate the short-term effects of a single session of tDCS in individuals who suffer from BN. In particular, we are interested in its effects on thought processes and emotions relating to food, eating, weight, and body shape. In the long term, this may help us to develop improved treatments for BN.

Why have I been invited?
You are invited to participate if you are a male or female aged between 18 and 70 who has a current diagnosis of bulimia nervosa (BN) or eating disorder not otherwise specified-bulimia type (EDNOS-BN). We will be recruiting 36 participants in total.

Do I have to take part?
You do not have to take part in this experiment; it is your choice. If you decide to take part you will be asked to sign a consent form. You will be free to withdraw from the study at any time without giving a reason. You may also withdraw any data or information you have already provided up until it is analysed for use in the final report. Whether you decide to take part or not will in no way influence your care or the timing of your treatment.

What will happen to me if I take part and what will I have to do?
If you decide you want to participate you will firstly be asked to engage in a telephone conversation with the experimenter (lasting approximately 20 minutes) to confirm that you are eligible to take part. If you are, you will be invited to the Institute of Psychiatry on a day that is convenient for both you and the researchers, in either the morning or the afternoon. You will be asked to return to the laboratory two more times, leaving a gap of at least 48 hours between each session. There is no need for any special preparation before the visits. Upon arrival to your first visit you will be asked to sign a consent form to confirm that you want to participate.



Each visit will take 1.5-2 hours and will involve completing a series of questionnaires (assessing mood and eating habits), a neuropsychological task (brain puzzle), and a food task for which you will be asked to rate different foods. You will not be required to eat any of these foods. You will also receive a 20-minute tDCS session, and have your blood pressure and pulse measured before and after. During the tDCS session you will sit on a comfortable chair and wear a plastic headband to keep the two electrodes in place (shown in the diagram on the right). The electrodes will be placed in small sponges soaked in a salt water solution, so they might feel a bit wet against your head. The researcher will turn the machine on which will deliver the currents. Two of the tDCS sessions you receive will be real and one will be a placebo (a fake session). The placebo session will be the same as the real sessions, but on this occasion the tDCS machine won't deliver any electrical current. Most people can't tell the difference between real and placebo tDCS sessions.

24 hours after each tDCS session the researcher will email you a short questionnaire to complete at your earliest convenience. This can be done over the telephone if you prefer.

Expenses and payments
Upon completion of your third visit you will be reimbursed £50 for your time and effort. This payment should be declared for tax and/or benefit purposes. Unfortunately we are not able to cover travel expenses except in exceptional circumstances.

What are the possible disadvantages and risks of taking part? What are the side effects?
There are no disadvantages or risks involved in taking part in this study; however, you may find the procedure slightly uncomfortable. This is because a number of sensations can occur beneath the electrodes during stimulation including tingling, pain, itching, and burning. Not everyone feels these sensations or finds them uncomfortable, but if you do remember you are free to stop the study at any point without giving an explanation. In

some rarer cases tDCS has been known to cause a headache, but this can be treated with mild painkillers (e.g. paracetamol).

What are the possible benefits of taking part?
Unfortunately there are no direct benefits to taking part in this study, but the information we get may help us to improve the treatment of BN in the future.

What happens when the research study stops?
When the research study stops no further tDCS sessions will be available.

What if there is a problem?
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making a decision.

PART TWO

What if relevant and new information becomes available?
Sometimes we get new information about the treatment being studied. This is not expected to occur given the very short time frame of participation (3 sessions over 5 days); however, if any new and relevant information becomes available during this time we will inform you immediately. You can then decide whether you wish to continue in the study.

What will happen if I don't want to carry on with the study?
If you decide to withdraw from the study there will be no adverse consequences. You may also withdraw any data or information you have already provided up until it is transcribed for use in the final report.

What if there is a problem?
If you have a concern about any aspect of the study, please ask the researchers (maria.kekic@kcl.ac.uk, 0207 848 0183) who will do their best to answer your questions. If you remain unhappy and wish to complain formally please contact Dr Gill Dale (director of research quality/head of joint South London and Maudsley NHS Foundation Trust and Institute of Psychiatry R&D Office) at Institute of Psychiatry P005, 16 De Crespigny Park, London, SE5 8AF. Should you wish to speak to someone outside of the university, the eating disorders charity Beat provides helplines for adults and young people which offer support and information to sufferers, carers and professionals. Further information can be found on their website (www.b-eat.co.uk).

Will my taking part in the study be kept confidential?
Your personal information and the data we collect from you will remain confidential at all times. It will also remain anonymous to everyone apart from the primary researchers. Manual files will be locked securely in a filing cabinet, which will be kept in a locked office, and all electronic files will be password protected. Your personal data will be destroyed 12 months after the study has ended.

Involvement of the General Practitioner (GP)

It is not necessary that we notify your GP of your participation in the study; however, you will be asked by the researcher whether you consent to us doing do. If you agree to this, you will be asked to provide us with your GP's contact details so that we can send them a letter with details of the research.

Involvement of the insurance company
If you have private medical insurance you should inform your insurance company that you are taking part in this study.

Will any genetic tests be done?
No.

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 has been collected. If you want written feedback of the study's findings you can contact the researcher (maria.kekic@kcl.ac.uk) for a lay summary. The results will be included in an examined postgraduate report, presented as part of a postgraduate presentation, and sent to a medical journal for publication. Your participation in the study will not be disclosed.

Who is organising and funding the research?
This study is being funded by King's College London.

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by City Road and Hampstead Ethics Committee.

Further information and contact details
If you have any questions or require more information about this study, please contact the researcher using the following contact details:

Maria Kekic (maria.kekic@kcl.ac.uk)
Department of Psychological Medicine
Section of Eating Disorders
Institute of Psychiatry, P059
16 De Crespigny Park
London, SE5 8AF

0207 848 0183

Appendix D.3 Information sheet for study of temporal discounting in healthy individuals

PARTICIPANT INFORMATION SHEET

KING'S College LONDON

Exploring the effects of motivational stimuli on proactive and reactive response inhibition.

Research Ethics Committee reference number: PNM/13/14-147

We would like to invite you to take part in this postgraduate research project. You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study. Please ask us if there is anything that is not clear or if you would like more information.

PART ONE

What is the purpose of the study?

There is a growing interest in psychiatry surrounding how humans control their behaviour. In particular, a lot of research is being done on two aspects of behavioural control: (1) delayed gratification (i.e., choosing between receiving a greater reward later compared to a smaller reward sooner), and (2) response inhibition. We are particularly interested in behavioural control in relation to eating disorders, as eating disorders are typically thought to lie along a continuum of atypical self-regulation. For example, people with Anorexia may have excessive behavioural control, whereas people with more impulsive eating behaviours such as binge-eating may have poor behavioural control.

While most studies of behavioural control have focused on *reactive* inhibition (i.e., cancelling a response following a "go" stimulus when one sees a latter "stop" cue), there has been little research into *proactive* inhibition (i.e. the process which generally suppresses responses until we are certain of the need to response. This proactive mechanism may be particularly important in the context of eating disorders, where cues predicting food-availability may trigger this process in an attempt to control food intake and food-related thoughts. While numerous studies have shown altered reactive inhibition in eating disorders, proactive inhibition has not yet been formally tested in this patient sample.

We are trying to develop an experiment that can be used to study proactive inhibition in eating disorders. Importantly, we first need to explore proactive inhibition in healthy people who do not have an eating disorder (or any other major psychiatric disorder).

In addition, we are interested in seeing how starvation affects your self control to get an idea of how this may be involved in the atypical behavioural control seen in eating disorders. We are also interested in seeing how food cues affect your ability to inhibit your responses. Food is a primary reward and generates a motivated emotional state. When you are hungry, food-related stimuli become even more motivationally-relevant. We are interested in seeing whether (a) motivational stimuli influence your ability to proactively or reactively inhibit behavioural responses, and (b) whether your motivational state affects the influence of these food-related stimuli. More specifically, we are exploring whether your performance is affected by food images when you are hungry (fasted state) compared to when you are not hungry (fed state).

Why have I been invited?

We have invited males and females to take part in this research who: (1) are aged over 18 years; (2) are of a healthy body weight (Body Mass Index (BMI) (kg/m^2): 18.5-24.9); and (3) have no current or previous history of any neurological or major psychiatric disorder.

Who must we exclude?

Unfortunately, we must ask you to *not* participate if you: (1) have a significant medical condition (e.g., a cardiovascular, neurological, or blood disorder); (2) are currently using illicit drugs; (3) are currently taking any psychotropic medication (e.g., antidepressants); (4) have a visual impairment that cannot be corrected (e.g., by glasses or contact lenses); (5) are pregnant, and (6) have insufficient knowledge of the English language, as this may compromise your understanding our assessments and questionnaires, which are not designed for people who might need extra help understanding what we are asking. Finally, (7) if you regularly consume a considerable amount of caffeine (i.e. tea, coffee, caffeinated soft-drinks) as you will be asked to refrain from consuming caffeine on the morning of the study and heavy consumers may experience some mild withdrawal symptoms.

The taking of drugs or medication may alter your behavioural responses, for example any drugs with sedative effects or caffeinated drinks, or medications whose effects may differ when you are fed compared to fasted and may interfere with what this study aims to measure. Lastly, because we require you not to eat on the morning of one of your visits, we ask that you have no serious medical condition and that you are not pregnant or breastfeeding for the purpose of your own safety.

Do I have to participate?

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 up to three copies of a consent form to show that you have agreed to take part: one for you to keep, one for us to keep, and one that will be sent to your GP (if you would like your GP to know of your involvement in the study).

If you do take part, you must agree that we can decide how to use the data. You are free to withdraw at any time, without giving a reason. If you withdraw from the study, you can tell us to destroy any information about you. It is of importance for you to know that, your treatment and care will not be affected, whether you decide to take part or not.

If you agree to take part you will be asked whether you are happy to be contacted about participation in future studies. Your participation in this study will not be affected should you choose not to be-recontacted.

If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form.

What will I have to do if I take part?

You will be asked to meet with the researcher on two separate occasions. Each session will last approximately 1 to 1.5 hours. During the first session, the researcher will explain the study to you and the instructions, and you will be given the opportunity to ask questions. If you are happy to continue, you will be asked to sign two copies of a consent form (one for you to keep).

On both sessions, you will be asked to complete a series of questionnaires pertaining to mood, personality and eating behaviours, followed by several computer-based tasks. Your weight, height and temperature will be measured, and you will have a small blood sample taken by a finger prick. This sample is to monitor your blood glucose.

On one of the sessions, you will be asked to avoid eating or drinking anything in the morning of the study. This will be your 'fasted' session. Both sessions will take place in the morning before noon, so that in your fasted session you will only be asked to skip breakfast.

Expenses and payments

You will receive £10 in compensation for each assessment day you complete (total £20) and can be reimbursed up to £5 for travel.

What is expected from you?
Apart from avoiding eating food on one visit, the expectations on you are minimal. We will ask that you avoid drinking alcohol the previous evening, and that you abstain from coffee on the morning of the scan, as caffeine, the active component in coffee, can influence your alertness and task performance. The tasks we are exploring are all relatively simple and are designed to measure your reaction times in different contexts.

What are the possible disadvantages and risks of participating in this study?
It is very unlikely that you will experience any discomfort from taking part in this research. You may find the finger prick slightly uncomfortable. This is a widely used procedure for obtaining blood samples. It takes only a second and we will only take a drop of blood from your index finger on your non-dominant hand. There is a small chance that you may find answering questions about mental health difficulties to be upsetting. However, you should remember that you do not have to answer any questions or give a blood sample if you do not want to and can withdraw from the study at any point without giving any explanation.

If you are pregnant you will not be able to participate in this study due to the effects of fasting on unborn children. You will be requested to inform the researcher of this information.

What are the possible benefits of taking part?
Taking part in this study will probably not benefit you directly. In the future, though, this research will help to develop tests and hypotheses for research in psychiatric and neurological disorders. 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.

Will my participation be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making a decision.

PART TWO

What if relevant and 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 will happen if I 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. You will be able to withdraw until data collection for this study is complete.

Will my 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.

We will only use your personal information to contact you if you have agreed to be contacted for participation in follow-up or future studies.

We will keep information about your identity secure for at least 10 years. Your data will be stored and analysed for as long as it can be used in research. Our data storage and analysis meets both current ethical guidelines and the conditions listed on the consent form.

What will happen to any samples I give?
We will collect blood samples on both days to monitor blood glucose levels. The samples will provide instant results and will be destroyed immediately after the reading is obtained. In the very unlikely event that an unusually high or low value was observed, we would inform you and advise you to contact your GP.

Will any genetic tests be done?
No, genetic tests will not be done. Blood samples are collected for monitoring blood glucose levels only.

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 an academic journal for publication, but you will not be identifiable. Your participation in the study will, of course, not be disclosed.

Who is organising and funding this research?
This study is being organised by a team of researchers at the Institute of Psychiatry, King's College London. It is being conducted as part of Ms Savani Bartholdy's (the principal investigator) 3 year postgraduate PhD programme and a dissertation project for a student on the MSc Neuroscience course. This project is funded by King's College London. The researchers in the study will not be paid for including you in this study.

Who has reviewed this study?
This study has been reviewed and approved by the Psychiatry, Nursing and Midwifery (PNM) Research Ethics Subcommittee (RESC) at King's College London.

Further information about the study and contact details:
General information about this research project can be obtained from Miss Savani Bartholdy, Section of Eating Disorders, Institute of Psychiatry, King's College London (Tel: 0207 848 0367 or Email: savani.bartholdy@kcl.ac.uk). If you have a concern about any aspects of the study, please contact Savani using the above contact details.
If this study has harmed you in any way or if you wish to make a complaint about the conduct of the study you can contact King's College London using the details below for further advice and information:

Dr Owen O'Daly
Centre for Neuroimaging Sciences,
Institute of Psychiatry,
De Crespigny Park,
London,
SE5 8AF
Email: o.o'daly@kcl.ac.uk

Tel: 0203228 3057,

General enquiries:

Savani Bartholdy (savani.bartholdy@kcl.ac.uk)
Department of Psychological Medicine
Section of Eating Disorders
Institute of Psychiatry, P059
16 De Crespigny Park
London, SE5 8AF

0207 848 0367

APPENDIX E: CONSENT FORMS

Appendix E.1 Consent form for study of tDCS in healthy individuals with frequent food cravings

CONSENT FORM FOR PARTICIPANTS IN RESEARCH STUDIES

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Title of Study: An investigation into the effects of transcranial direct current stimulation (tDCS) on food cravings and self-regulation in healthy women

King's College Research Ethics Committee Ref: PNM/12/13-112

Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

Please tick

- I understand that if I decide at any time during the research that I no longer wish to participate in this project, I can notify the researchers involved and withdraw from it immediately without giving any reason. Furthermore, I understand that I will be able to withdraw my data up until it is transcribed for use in the final report (30/06/13). ☐
- I consent to the processing of my personal information for the purposes explained to me. I understand that such information will be handled in accordance with the terms of the UK Data Protection Act 1998. ☐

- I have read and understood the information sheet provided. ☐
- I agree to be contacted in the future by King's College London researchers who would like to invite me to participate in follow up studies to this project, or in future studies of a similar nature. ☐
- I understand that confidentiality and anonymity will be maintained and it will not be possible to identify me in any publications ☐
- I understand that I must not take part if I have any of the conditions listed in the exclusion criteria ☐

Participant's Statement:

I _____

agree that the research project named above has been explained to me to my satisfaction and I agree to take part in the study. I have read both the notes written above and the Information Sheet about the project, and understand what the research study involves.

Signed **Date**

Investigator's Statement:

I _____

Confirm that I have carefully explained the nature, demands and any foreseeable risks (where applicable) of the proposed research to the participant.

Signed **Date**

Appendix E.2 Consent form for study of tDCS in patients with BN

CONSENT FORM FOR PARTICIPANTS IN RESEARCH STUDIES

Please complete this form after you have read the information sheet and listened to an explanation about the research.

KING'S College LONDON

Title of Study: An investigation into the effects of transcranial direct current stimulation (tDCS) in anorexia nervosa and bulimia nervosa

Research Ethics Committee reference number: 14/LO/0025

Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the information sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this consent form to keep and refer to at any time.

Please initial

- I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected. I understand that I will be able to withdraw my data up until it is analysed for use in the final report. ☐
- I consent to the processing of my personal information for the purposes explained to me. I understand that such information will be handled in accordance with the terms of the UK Data Protection Act 1998. I understand that confidentiality and anonymity will be maintained and it will not be possible to identify me in any publications ☐
- I have read and understood the information sheet provided. I have had the opportunity to consider the information and ask questions. ☐
- I understand that I must not take part if I have any of the conditions listed in the exclusion criteria ☐

- I agree to my GP being informed of my participation in this study ☐
- I agree to take part in the above study ☐

Participant's Statement:

I _____
agree that the research project named above has been explained to me to my satisfaction and I agree to take part in the study. I have read both the notes written above and the Information Sheet about the project, and understand what the research study involves.

Signed **Date**

Investigator's Statement:

I _____
Confirm that I have carefully explained the nature, demands and any foreseeable risks (where applicable) of the proposed research to the participant.

Signed **Date**

Appendix E.3 Consent form for study of temporal discounting in healthy individuals

CONSENT FORM FOR PARTICIPANTS IN RESEARCH STUDIES

Please complete this form after you have read the information sheet and listened to an explanation about the research.

KING'S College LONDON

Title of Study: Exploring the effects of motivational stimuli on proactive and reactive response inhibition.

Research Ethics Committee reference number: PNM/13/14-147

Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the information sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this consent form to keep and refer to at any time.

Please initial

- I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason, without my legal rights being affected. I understand that I will be able to withdraw my data up until it is transcribed for use in the final report. ☐
- I have read and understood the information sheet provided. I have had the opportunity to consider the information and ask questions. ☐

- I understand that my data will be handled in accordance with the terms of the UK Data Protection Act 1998. I understand that confidentiality and anonymity will be maintained and it will not be possible to identify me in any publications.

- I agree that the research team may use my data for future research and understand that any such use of identifiable data would be reviewed and approved by a research ethics committee. (In such cases, as with this project, data would not be identifiable in any report). ☐

- I understand that I must not take part if I have any of the conditions listed in the exclusion criteria.

- I agree that the investigators will take a sample of my blood. I understand that these samples will be used to assess glucose level. I understand that I may not receive any information about my individual results.

- I know that if I would like to, I can contact the research team and request a written summary of findings of the study.

- I **consent/do not consent** to be contacted in the future by King's College London researchers who would like to invite me to participate in follow up studies to this project, or in future studies of a similar nature.

- I agree to take part in the above study ☐

Participant's Statement:

I _____ agree that the research project named above has been explained to me to my satisfaction and I agree to take part in the study. I have read both the notes written above and the Information Sheet about the project, and understand what the research study involves.

Signed **Date**

Investigator's Statement:

I _____ confirm that I have carefully explained the nature, demands and any foreseeable risks (where applicable) of the proposed research to the participant.

Signed **Date**

Enquiries:
Savani Bartholdy
P059, Section of Eating Disorders,
Institute of Psychiatry,
De Crespigny Park,
London, SE5 8AF,

Phone: 0207 848 0367
Email: savani.bartholdy@kcl.ac.uk

APPENDIX F: SCREENING MEASURES

Appendix F.1 Inclusion/exclusion criteria for study of tDCS in healthy individuals with frequent food cravings

Do you have frequent food cravings?	Yes	No
Which foods do you crave the most?		
How many times each day do you have a food craving?		
Have you been diagnosed with an eating disorder? If yes, which one and when?	Yes	No
Have you been diagnosed with another psychiatric disorder (e.g. depression, anxiety, schizophrenia, panic disorder)? If yes, which one and when?	Yes	No
Have you had any significant health problems in the past 6 months (e.g. diabetes, asthma, chronic pain, heart problems)? If yes, provide more details	Yes	No
Have you had any blood tests in the past month? If yes, were there any abnormal results?	Yes Yes	No No
Do you have any food allergies? If yes, provide details	Yes	No
Do you smoke more than 10 cigarettes per day?	Yes	No
Do you drink alcohol? If yes, how much?	Yes _____ days per week	No _____ drinks per day
Do you take drugs?	Yes	No

Do you have a current GP? If yes, are you happy for us to contact them in an emergency? If yes, provide name of GP and GP practice	Yes No Yes No
Are you pregnant?	Yes No
Do you take the contraceptive pill? If yes, which one?	Yes No
When was your last period?	
Height	
Weight	
BMI (office use only)	

Appendix F.2 Inclusion/exclusion criteria for study of tDCS in patients with BN

Have you been diagnosed with an eating disorder?	Yes No Which one _____ When _____
Have you been diagnosed with another psychiatric disorder (e.g. depression, anxiety, schizophrenia, panic disorder)? If yes, which one and when?	Yes No
Have you had any significant health problems in the past 6 months (e.g. diabetes, asthma, chronic pain, heart problems)? If yes, provide more details	Yes No

Have you had any blood tests in the past month?	Yes	No
If yes, were there any abnormal results?	Yes	No
Do you smoke more than 15 cigarettes per day?	Yes	No
Do you drink alcohol?	Yes	No
If yes, how much?	_____ days per week _____ drinks per day	
Do you take drugs?	Yes	No
Do you have a current GP?	Yes	No
If yes, are you happy for us to contact them?	Yes	No
If yes, provide name of GP and GP practice		
Are you pregnant?	Yes	No
Do you take the contraceptive pill?	Yes	No
When was your last period?		
Height		
Weight		
BMI (office use only)		

Appendix F.3 Inclusion/exclusion criteria for study of temporal discounting in healthy individuals

1. Have you ever been diagnosed with an eating disorder?	**YES**	**NO**
2. 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?)		
3. Have you ever had any neurological disease (eg stroke), brain or eye injury or any brain surgery? ….. if YES please provide more details?	**YES**	**NO**
4. Do you experience regular headaches, migraines, dizzy or fainting spells, double or blurred vision, numbness or tingling, or problems with balance? ….. if YES please provide more details?	**YES**	**NO**
5. Have you had blood tests done in the past month? ….if YES where and were there any abnormal results?	**YES**	**NO**
6. Do you smoke more than 5 cigarettes/day?	**YES**	**NO**
7. How much caffeine do you drink? ….. if YES what type? (eg. coffee, tea, coke)	**……..days/wk** **……..drinks/day**	
7. How much alcohol do you drink? ….. if YES what type? (eg. wine, beer, spirits) How many units do you drink per week? (NB. 1 unit = 25ml spirits or half a pint of beer, 1.5units = 125ml wine)	**……..days/wk** **……..dinks/day** **……..units/week**	
8. Do you take drugs?	**YES**	**NO**
9. Are you currently taking any medication? ….if YES which one and for how long?	**YES**	**NO**
10. Are you currently receiving any psychological/psychiatric treatment?	**YES**	**NO**
13. Are you pregnant?	**YES**	**NO**
14. Are you currently on a diet? If yes, please describe.	**YES**	**NO**
15. What is your current weight?		**kg**

16. What is your current height?	**cm**

Meal	Never	Rarely	Some days	Most days	Everyday
Breakfast					
Describe:					
Mid morning snack					
Describe:					
Lunch					
Describe:					
Afternoon snack					
Describe:					
Dinner					
Describe:					
Evening snack					
Describe:					

Appendix F.4 Structured Clinical Interview for Diagnostic and Statistical Manual Disorders (SCID)

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 drug use, work, family, friends, financially) or; b) someone else objected to you taking street drugs or thought they 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 6 months have you been particularly nervous or anxious? Do you worry a lot about bad things that 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 GAD
4. Have you ever had periods of time when you were feeling depressed or down most of the day nearly every day? Or periods of 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 you thought about hurting yourself? Or had times when you've thought about death or even wished you were dead?	1	2	3 Screener only - if yes assess risk to self/others
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
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	1	2	3

them? 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	If yes circle **yes** on **F.20** and assess for obsession
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 **A.18** 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, 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? If yes, what traumatic event(s) have you experienced? Sometimes after experiencing very upsetting events like 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 the traumatic event(s) you experienced?	1 2 3 1: No 2. Yes, but not in the past 12 months 3. Yes, in the past 12 months 1 2 3 1: No 2. Yes, but not in the past 12 months 3. Yes, 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 **G.13** and assess for BDD
17. 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 hear, or seen things that other people could not see?	1 2 3 Screener only - if yes assess risk to self/others

Appendix F.5 tDCS safety screen

Have you ever:

Had an adverse reaction to tDCS?	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 □
Had any brain-related condition?	Yes □	No □
Had any illness that caused brain injury?	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 □
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 tDCS and its associated risks?	Yes □	No □

If you answered **yes** to any of the above, please provide details:

Appendix F.6 Eating Disorder Diagnostic Scale (EDDS)

During 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 tub 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 – 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?

_____

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?

_____

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?

_____

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?

_____

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?

_____

---

19. How much do you weigh? If uncertain, please give your best estimate.

_____

20. How tall are you? If uncertain, please give your best estimate.

_____

21. Over the past **3 months**, how many menstrual periods have you missed?

_____ (0 – 3)

22. Have you been taking birth control pills during the past **3 months**?

YES NO

APPENDIX G: EXPERIMENTAL MEASURES

Appendix G.1 Demographic questionnaire for study of tDCS in healthy individuals with frequent food cravings

Full name	
Gender	
Date of birth	
Age	
Occupation	
Highest level of education completed (please circle)	GCSE AS Level A Level Bach. degree Masters PhD
Marital status (please circle)	Single Married Divorced Engaged Widowed Other
Ethnicity (please circle)	White Mixed Asian Black Chinese Arab Other
Number of children/dependents	
How many meals do you eat per day?	
How many snacks do you eat per day?	

Appendix G.2 Demographic questionnaire for study of tDCS in patients with BN

Full name	
Gender	

Date of birth	
Age	
Occupation	
Annual personal income (please circle)	£19,999 or less £20,000 - £39,999 £40,000 - 59,999 £60,000 - £79,999 £80,000 - £99,999 £100,000 or more
Highest level of education completed (please circle)	GCSE AS Level A Level Bach. degree Masters PhD
Marital status (please circle)	Single Married Divorced Engaged Widowed Other
Ethnicity (please circle)	White Mixed Asian Black Chinese Arab Other
Number of children/dependents	
Handedness	Right handed Left handed
Diet (please circle)	Vegetarian Vegan Neither
Number of meals/snacks per day	Meals_____ Snacks_____
Do you take any medications? **If yes, which ones and what for?**	Yes No
Do you have a current GP? **If yes, would you like us to inform them of your participation in this study?** **If yes, provide contact details.**	Yes No Yes No
Do you have a current psychological therapist? **If yes, would you like us to inform them of your participation in this study?** **If yes, provide contact details.**	Yes No Yes No

Appendix G.3 Demographic questionnaire for study of temporal discounting in healthy individuals

1. Name……..

2. Address……

3. Contact telephone no……..

4. Email……..

5. Age…….. 6. D.O.B……..

7. Height…….. 8. Weight…… 9. BMI……..

10. Ethnicity……..

11. Occupation……

12. Marital Status……

13. No. of children (if any)……..

Appendix G.4 Eating Disorder Examination-Questionnaire (EDE-Q)

The following questions are concerned with the past four weeks (28 days) only. Please read each question carefully. **Please answer all the questions.**

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

	On how many of the past 28 days...	**No days**	**1-5 days**	**6-12 days**	**13-15 days**	**16-22 days**	**23-27 days**	**Every day**
1	Have you been deliberately trying to limit the amount of food you eat to influence your shape or weight (whether or not you have succeeded)?	0	1	2	3	4	5	6

2	Have you gone for long periods of time (8 waking hours or more) without eating anything at all in order to influence your shape or weight?	0	1	2	3	4	5	6
3	Have you tried to exclude from your diet any foods that you like in order to influence your shape or weight (whether or not you have succeeded)?	0	1	2	3	4	5	6
4	Have you tried to follow definite rules regarding your eating (for example, a calorie limit) in order to influence your shape or weight (whether or not you have succeeded)?	0	1	2	3	4	5	6
5	Have you had a definite desire to have an empty stomach with the aim of influencing your shape or weight?	0	1	2	3	4	5	6
6	Have you had a definite desire to have a totally flat stomach?	0	1	2	3	4	5	6
7	Has thinking about food, eating or calories made it very difficult to concentrate on things you are interested in (for example, working, following a conversation, or reading)?	0	1	2	3	4	5	6
8	Has thinking about shape or weight made it very difficult to concentrate on things you are interested in (for example, working, following a conversation, or reading)?	0	1	2	3	4	5	6
9	Have you had a definite fear of losing control over eating?	0	1	2	3	4	5	6
10	Have you had a definite fear that you might gain weight?	0	1	2	3	4	5	6
11	Have you felt fat?	0	1	2	3	4	5	6
12	Have you had a strong desire to lose weight?	0	1	2	3	4	5	6

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

13	Over the past 28 days, how many times have you eaten what other people would regard as an unusually large amount of food (given the circumstances)?	
14	… On how many of these times did you have a sense of having lost control over your eating (at the time you were eating)?	

15	Over the past 28 days, on how many DAYS have such episodes of overeating occurred (i.e. you have eaten an unusually large amount of food and have had a sense of loss of control at the time)?	
16	Over the past 28 days, how many times have you made yourself sick (vomit) as a means of controlling your shape or weight?	
17	Over the past 28 days, how many times have you taken laxatives as a means of controlling your shape or weight?	
18	Over the past 28 days, how many times have you exercised in a "driven" or "compulsive" way as a means of controlling your weight, shape or amount of fat, or to burn off calories?	

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

		No days	**1-5 days**	**6-12 days**	**13-15 days**	**16-22 days**	**23-27 days**	**Every day**
19	Over the past 28 days, on how many days have you eaten in secret (ie, furtively)? … Do not count episodes of binge eating.	0	1	2	3	4	5	6
		None of the times	**A few of the times**	**Less than half**	**Half of the times**	**More than half**	**Most of the time**	**Every time**
20	On what proportion of the times that you have eaten have you felt guilty (felt that you've done wrong) because of its effect on your shape or weight? … Do not count episodes of binge eating.	0	1	2	3	4	5	6
		Not at all		**Slightly**		**Moderately**		**Markedly**
21	Over the past 28 days, how concerned have you been about other people seeing you eat? … Do not count episodes of binge eating.	0	1	2	3	4	5	6

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

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

Appendix G.5 Depression Anxiety and Stress Scales (DASS-21)

DASS21

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you *over the past week*. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

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.6 Food Craving Questionnaire-Trait (FCQ-T)

Below is a list of comments made by people about their eating habits. In the space to the left, please write the number indicating how frequently these comments would be true for you in general. Please respond to each item as honestly as possible.

Never or not applicable	Rarely	Sometimes	Often	Usually	Always
(1)	(2)	(3)	(4)	(5)	(6)

_____ 1. Being with someone who is eating often makes me hungry.
_____ 2. When I crave something, I know I won't be able to stop eating once I start.
_____ 3. If I eat what I am craving, I often lose control and eat too much.
_____ 4. I hate it when I give into cravings.
_____ 5. Food cravings invariably make me think of ways to get what I want to eat.
_____ 6. I feel like I have food on my mind all the time.
_____ 7. I often feel guilty for craving certain foods.
_____ 8. I find myself preoccupied with food.
_____ 9. I eat to feel better.
_____ 10. Sometimes, eating makes things seem just perfect.
_____ 11. Thinking about my favorite foods makes my mouth water.
_____ 12. I crave foods when my stomach is empty.
_____ 13. I feel as if my body asks me for certain foods.
_____ 14. I get so hungry that my stomach seems like a bottomless pit.
_____ 15. Eating what I crave makes me feel better.
_____ 16. When I satisfy a craving I feel less depressed.
_____ 17. When I eat what I am craving I feel guilty about myself.
_____ 18. Whenever I have cravings, I find myself making plans to eat.
_____ 19. Eating calms me down.
_____ 20. I crave foods when I feel bored, angry, or sad.
_____ 21. I feel less anxious after I eat.
_____ 22. If I get what I am craving I cannot stop myself from eating it.
_____ 23. When I crave certain foods, I usually try to eat them as soon as I can.
_____ 24. When I eat what I crave I feel great.
_____ 25. I have no will power to resist my food crave.
_____ 26. Once I start eating, I have trouble stopping.
_____ 27. I can't stop thinking about eating no matter how hard I try.
_____ 28. I spend a lot of time thinking about whatever it is I will eat next.
_____ 29. If I give in to a food craving, all control is lost.
_____ 30. When I'm stressed out, I crave food.
_____ 31. I daydream about food.
_____ 32. Whenever I have a food craving, I keep on thinking about eating until I actually eat the food.
_____ 33. If I am craving something, thoughts of eating it consume me.
_____ 34. My emotions often make me want to eat.
_____ 35. Whenever I go to a buffet I end up eating more that what I needed.
_____ 36. It is hard for me to resist the temptation to eat appetizing foods that are in my reach.
_____ 37. When I am with someone who is overeating, I usually overeat too.
_____ 38. When I eat food, I feel comforted.
_____ 39. I crave foods when I'm upset.

Appendix G.7 Food Craving Questionnaire-State (FCQ-S)

Below is a list of comments made by people about their eating habits. In the space to the left, please write the number indicating how much you agree with the comment right now, at this very moment. Notice that some questions refer to foods in general while others refer to one or more specific foods. Please respond to each item as honestly as possible.

Strongly disagree	Disagree	Neutral	Agree	Strongly agree
(1)	(2)	(3)	(4)	(5)

____ 1. I have an intense desire to eat [one or more specific foods].
____ 2. I'm craving [one or more specific foods].
____ 3. I have an urge for [one or more specific foods].
____ 4. Eating [one or more specific foods] would make things seem just perfect.
____ 5. If I were to eat what I am craving, I am sure my mood would improve.
____ 6. Eating [one or more specific foods] would feel wonderful.
____ 7. If I ate something I wouldn't feel so sluggish and lethargic.
____ 8. Satisfying my craving would make me feel less grouchy and irritable.
____ 9. I would feel more alert if I could satisfy my craving.
____ 10. If I had [one or more specific foods], I could not stop eating it.
____ 11. My desire to eat [one or more specific foods] seems overpowering.
____ 12. I know I'm going to keep on thinking about [one or more specific foods] until I actually have it.
____ 13. I am hungry.
____ 14. If I ate right now, my stomach wouldn't feel as empty.
____ 15. I feel weak because of not eating.

Appendix G.8 Food Challenge Task (FCT) for study of tDCS in healthy individuals with frequent food cravings

1. Please mark the following lines at the point that most accurately reflects 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 like to eat them very much

Would not like to eat them at all

2. Please mark the following lines at the point that most accurately reflects 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 like to eat them very much

Would not like to eat them at all

3. Please mark the following lines at the point that most accurately reflects 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 like to eat them very much

Would not like to eat them at all

4. Please mark the following lines at the point that most accurately reflects 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 like to eat them very much — Would not like to eat them at all

5. Please mark the following line at the point that most accurately reflects your current level of stress.

Not stressed at all — Extremely stressed

6. Looking at the foods in front of you, please mark the following line at the point that most accurately reflects your current level of anxiety.

Not anxious at all — Extremely anxious

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 (on any, or all, of these foods).

No urge to binge at all ——————————— Extremely strong urge to binge

Appendix G.9 Delaying Gratification Inventory (DGI)

Please rate the extent to which you agree with each of the following statements, using the scale provided. Please circle an answer according to what *really* reflects your experience rather than what you think your experience should be.

		Strongly disagree	**Moderately disagree**	**Neither agree nor disagree**	**Moderately agree**	**Strongly agree**
1	I can resist junk food when I want to.	1	2	3	4	5
2	I am able to control my physical desires.	1	2	3	4	5
3	I hate having to take turns with other people.	1	2	3	4	5
4	When I am able to, I try to save away a little money in case an emergency should arise.	1	2	3	4	5
5	I worked hard in school to improve myself as a person.	1	2	3	4	5

6	I would have a hard time sticking with a special, healthy diet.	1	2	3	4	5
7	I like to get to know someone before having a physical relationship.	1	2	3	4	5
8	Usually I try to consider how my actions affect others.	1	2	3	4	5
9	It is hard for me to resist buying things I cannot afford.	1	2	3	4	5
10	I have tried to work hard in school so that I could have a better future.	1	2	3	4	5
11	If my favourite food were in front of me, I would have a difficult time waiting to eat it.	1	2	3	4	5
12	My habit of focusing on what “feels good” has cost me in the long run.	1	2	3	4	5
13	I think that helping each other benefits society.	1	2	3	4	5
14	I try to spend my money wisely.	1	2	3	4	5
15	In school, I tried to take the easy way out.	1	2	3	4	5
16	It is easy for me to resist candy and bowls of snack foods.	1	2	3	4	5
17	I have given up physical pleasure or comfort to reach my goals.	1	2	3	4	5
18	I try to consider how my actions will affect other people in the long-term.	1	2	3	4	5
19	I cannot be trusted with money.	1	2	3	4	5
20	I am capable of working hard to get ahead in life.	1	2	3	4	5

21	Sometimes I eat until I make myself sick.	1	2	3	4	5
22	I prefer to explore the physical side of romantic involvements right away.	1	2	3	4	5
23	I do not consider how my behaviour affects other people.	1	2	3	4	5
24	When someone gives me money, I prefer to spend it right away.	1	2	3	4	5
25	I cannot motivate myself to accomplish long-term goals.	1	2	3	4	5
26	I have always tried to eat healthy because it pays off in the long run.	1	2	3	4	5
27	When faced with a physically demanding chore, I always tried to put off doing it.	1	2	3	4	5
28	I value the needs of other people around me.	1	2	3	4	5
29	I manage my money well.	1	2	3	4	5
30	I have always felt like my hard work would pay off in the end.	1	2	3	4	5
31	Even if I am hungry, I can wait until it is meal time before eating something.	1	2	3	4	5
32	I have lied or made excuses in order to go do something more pleasurable.	1	2	3	4	5
33	There is no point in considering how my decisions affect other people.	1	2	3	4	5
34	I enjoy spending money the moment I get it.	1	2	3	4	5
35	I would rather take the easy road in life than get ahead.	1	2	3	4	5

Appendix G.10 Profile of Mood States (POMS)

Please describe how you feel RIGHT NOW, using the scale provided. Please circle an answer that reflects how you *really* feel, rather than how you think you should feel.

	Feeling	**Not at all**		**Moderately**		**Extremely**
1	Friendly	0	1	2	3	4
2	Tense	0	1	2	3	4
3	Angry	0	1	2	3	4
4	Worn out	0	1	2	3	4
5	Unhappy	0	1	2	3	4
6	Clear-headed	0	1	2	3	4
7	Lively	0	1	2	3	4
8	Confused	0	1	2	3	4
9	Sorry for things done	0	1	2	3	4
10	Shaky	0	1	2	3	4
11	Listless (impassive, lack of energy)	0	1	2	3	4
12	Peeved (annoyed, resentful)	0	1	2	3	4
13	Considerate	0	1	2	3	4
14	Sad	0	1	2	3	4
15	Active	0	1	2	3	4
16	On edge	0	1	2	3	4
17	Grouchy	0	1	2	3	4
18	Blue	0	1	2	3	4
19	Energetic	0	1	2	3	4
20	Panicky	0	1	2	3	4
21	Hopeless	0	1	2	3	4
22	Relaxed	0	1	2	3	4
23	Unworthy	0	1	2	3	4
24	Spiteful	0	1	2	3	4
25	Sympathetic	0	1	2	3	4
26	Uneasy	0	1	2	3	4
27	Restless	0	1	2	3	4
28	Unable to concentrate	0	1	2	3	4
29	Fatigued	0	1	2	3	4

30	Helpful	0	1	2	3	4
31	Annoyed	0	1	2	3	4
32	Discouraged	0	1	2	3	4
33	Resentful	0	1	2	3	4
34	Nervous	0	1	2	3	4
35	Lonely	0	1	2	3	4
36	Miserable	0	1	2	3	4
37	Muddled	0	1	2	3	4
38	Cheerful	0	1	2	3	4
39	Bitter	0	1	2	3	4
40	Exhausted	0	1	2	3	4
41	Anxious	0	1	2	3	4
42	Ready to fight	0	1	2	3	4
43	Good-natured	0	1	2	3	4
44	Gloomy	0	1	2	3	4
45	Desperate	0	1	2	3	4
46	Sluggish	0	1	2	3	4
47	Rebellious	0	1	2	3	4
48	Helpless	0	1	2	3	4
49	Weary	0	1	2	3	4
50	Bewildered	0	1	2	3	4
51	Alert	0	1	2	3	4
52	Deceived	0	1	2	3	4
53	Furious	0	1	2	3	4
54	Efficient	0	1	2	3	4
55	Trusting	0	1	2	3	4
56	Full of pep (full of energy, full of drive)	0	1	2	3	4
57	Bad-tempered	0	1	2	3	4
58	Worthless	0	1	2	3	4
59	Forgetful	0	1	2	3	4
60	Carefree	0	1	2	3	4
61	Terrified	0	1	2	3	4
62	Guilty	0	1	2	3	4
63	Vigorous	0	1	2	3	4
64	Uncertain about things	0	1	2	3	4

65	Bushed (tired out, exhausted)	0	1	2	3	4

Appendix G.11 Positive and Negative Affect Schedule (PANAS)

Please describe how you feel RIGHT NOW, using the scale provided. Please circle an answer that reflects how you *really* feel, rather than how you think you should feel.

	Feeling	**Very slightly or not at all**	**A little**	**Moderately**	**Quite a bit**	**Extremely**
1	Interested	1	2	3	4	5
2	Distressed	1	2	3	4	5
3	Excited	1	2	3	4	5
4	Upset	1	2	3	4	5
5	Strong	1	2	3	4	5
6	Guilty	1	2	3	4	5
7	Scared	1	2	3	4	5
8	Hostile	1	2	3	4	5
9	Enthusiastic	1	2	3	4	5
10	Proud	1	2	3	4	5
11	Irritable	1	2	3	4	5
12	Alert	1	2	3	4	5
13	Ashamed	1	2	3	4	5
14	Inspired	1	2	3	4	5
15	Nervous	1	2	3	4	5
16	Determined	1	2	3	4	5
17	Attentive	1	2	3	4	5
18	Jittery	1	2	3	4	5
19	Active	1	2	3	4	5
20	Afraid	1	2	3	4	5

Appendix G.12 Mize's Eating Disorder Examination Questionnaire-Revised (MEDCQ-R)

This is an inventory of beliefs and attitudes about eating and weight. There are a number of statements with which you may tend to agree or disagree. For each statement, please circle one of the numbers according to your own reaction to the item.

It is not necessary to think over any item very long. Mark you answer quickly and go on to the next statement.

Be sure to mark how you actually feel about the statement, not how you think you should feel.

Try to avoid the neutral or "3" response as much as possible. Select this answer only if you really cannot decide whether you tend to agree or disagree with a statement.

		Strongly disagree	**Moderately disagree**	**Neither agree nor disagree**	**Moderately agree**	**Strongly agree**
1	I feel victorious over my hunger when I am able to refuse sweets.	1	2	3	4	5
2	No matter how much I weigh, fats, sweets, breads, and cereals are bad food because they always turn into fat.	1	2	3	4	5
3	No one likes fat people; therefore, I must remain thin to be liked by others.	1	2	3	4	5
4	I am proud of myself when I control my urge to eat.	1	2	3	4	5
5	When I eat desserts, I get fat. Therefore, I must never eat desserts so I won't be fat.	1	2	3	4	5
6	How much I weigh has little to do with how popular I am	1	2	3	4	5
7	If I don't establish a daily routine, everything will be chaotic and I won't accomplish anything.	1	2	3	4	5
8	My friends will like me regardless of how much I weigh.	1	2	3	4	5

9	When I am overweight, I am not happy with my appearance. Gaining weight will take away the happiness I have with myself.	1	2	3	4	5
10	People like you because of your personality, not whether you are overweight or not.	1	2	3	4	5
11	When I eat something fattening, it doesn't bother me that I have temporarily let myself eat something I'm not supposed to.	1	2	3	4	5
12	If I eat a sweet, it will be converted instantly into stomach fat.	1	2	3	4	5
13	If my weight goes up, my self-esteem goes down.	1	2	3	4	5
14	I can't enjoy anything because it will be taken away.	1	2	3	4	5
15	It is more important to be a good person than it is to be thin.	1	2	3	4	5
16	When I see someone who is overweight, I worry that I will be like him/her.	1	2	3	4	5
17	All members of the opposite sex want a mate who has a perfect, thin body.	1	2	3	4	5
18	Having a second serving of a high calorie food I really like doesn't make me feel guilty.	1	2	3	4	5
19	If I can cut out all carbohydrates, I will never be fat.	1	2	3	4	5
20	When I overeat, it has no effect on whether or not I feel like a strong person.	1	2	3	4	5
21	Members of the opposite sex are more interested in "who" you are rather than whether or not you are thin.	1	2	3	4	5
22	If I gain one pound, I'll go on and gain a hundred pounds, so I must keep precise control of my weight, food, and exercise.	1	2	3	4	5

23	I rarely criticize myself if I have let my weight go up a few pounds.	1	2	3	4	5
24	I try to attract members of the opposite sex through my personality rather than by being thin.	1	2	3	4	5

Appendix G.13 Tolerability questionnaire

Please mark the following line at the point that most accurately reflects how much <u>discomfort</u> you experienced during your tDCS session.

No discomfort at all ——————————————— Extreme discomfort

Appendix G.14 Acceptability questionnaire

1. If a therapeutic trial of tDCS were available, would you be happy to take part? A therapeutic trial would typically involve 20 sessions of tDCS over 4 weeks. (Please circle)

Yes No

2. If no, why would you not be happy to take part? (Please select all that apply).

I found it too painful/uncomfortable □
I wouldn't be able to commit to so many sessions □
I don't think it would be helpful for me □
I think it would do more harm than good □
Other □ (please state)

_____

_____

_____

Appendix G.15 Test of blinding

1. One/two of your tDCS sessions was/were real and one was a placebo. Which session do you think was the placebo session? (Please circle)

Session one Session two Session three[17]

2. How sure are you of this?

Completely unsure _____ Extremely sure

[17] This was deleted for the study of tDCS in healthy individuals with frequent food cravings.

APPENDIX H: OTHER

Appendix H.1 Berner and Marsh (2014) neurobiological model of BN