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An Investigation of Concurrent Attention Bias Modification Training and Self-Administered Transcranial Direct Current Stimulation in Binge Eating Disorder

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King's College London

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An Investigation of Concurrent Attention Bias Modification Training and Self-Administered Transcranial Direct Current Stimulation in Binge Eating Disorder

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Institute of Psychiatry, Psychology & Neuroscience

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

Doctor of Philosophy (PhD)

2022

Dedicated with love to Renate.

A woman with spark.

Abstract

Binge eating disorder (BED) is common, yet treatment options are suboptimal. Novel treatments may yield better outcomes than established approaches if they directly target the mechanisms involved in the maintenance of BED. Neurobiological models have implicated altered cognitive control, and recent studies have indicated that attention bias (AB) towards high-calorie food may be a potent target for treatment. Accordingly, interventions that directly target cognitive control functions have been developed. These include attention bias modification training (ABMT), a computerised training programme that aims to reduce the strength of an implicit AB towards high-calorie food cues, and transcranial direct current stimulation (tDCS), a non-invasive brain stimulation (NIBS) technique that uses direct current electric fields to alter cortical excitability and enhance neuroplasticity. Independently, both ABMT and tDCS have been reported to produce therapeutic effects in patients with BED, however, it is proposed that the effects of tDCS may be enhanced when disorder-related brain regions are activated during stimulation, and that the effects of ABMT may be improved when neuroplasticity is greater. Thus, outcomes from treatment may be superior when tDCS and ABMT are combined.

To better understand the potential for tDCS to influence AB, we first reviewed the literature relating to the effects of NIBS on AB towards emotion. Here, we reveal that, although the evidence is mixed, findings in clinical populations generally suggest that AB may be altered by NIBS. In parallel, a cross sectional study of food-related AB in obesity with and without BED examined the extent to which AB was a distinct feature of BED. We observed that both groups showed AB towards high-calorie food cues, but that only participants with BED showed a bias towards low-calorie food cues, and that the relationship between craving and food-related AB was greatest in BED. Accordingly, we conducted a feasibility trial of concurrent at-home tDCS with ABMT in adults with BED. Findings indicated that the study protocol is feasible, and that the intervention is acceptable. Moreover, tDCS with ABMT was associated with reductions in objective binge eating behaviour, craving, and AB towards high-calorie food stimuli which were maintained to follow-up. As a result, concurrent tDCS with ABMT is a promising novel option for treatment, and future trials of this approach are encouraged.

COVID-19 Impact Statement

Due to the COVID-19 global pandemic, the randomised controlled trial that was intended to be the primary focus for this thesis could not go ahead. Prior to the first national lockdown in March 2020, the candidate and her supervisors had completed a protocol for a two-part study of the effects of intermittent theta burst stimulation (iTBS) in adults and adolescents with binge eating disorder (BED). Part one was a randomised sham-controlled trial that would have examined the effect of a single-session of neuronavigated iTBS targeting the left dorsolateral prefrontal cortex on mood, emotion regulation, craving, and food consumption in adults and adolescents with binge eating disorder (n = 68). Part-two would have been a case-series assessing the therapeutic effects of 20-sessions of real neuronavigated iTBS targeting the left dorsolateral prefrontal cortex in adults and adolescents (n = 20) with follow-up to three-months post-treatment.

The candidate applied for approval to undertake this research in October 2019, and all necessary approvals were awarded by the Leeds NHS Research Ethics Committee on the 4th of May 2020 and Health Research Authority on the 5th of June 2020. However, as we were unable to make adequate adaptations to trial procedures to accommodate safe social distancing, the candidate and her supervisors decided that it was not the right time to move forward with this trial. A copy of the protocol for this study and associated approval letters are provided in Appendix J and we hope that this trial will go ahead in the future.

Acknowledgements

To my supervisors, Professor Ulrike Schmidt and Professor Iain Campbell, I am immensely grateful for the guidance and opportunities you have given me in the last few years – I can't imagine having navigated this journey without your unwavering belief in my ability or your spirit of innovation. Ulrike, it is an enormous privilege to have you as a mentor; you are an inspiration and you have shown me that it is possible to thrive as both a clinician and a researcher. Thank you for being so generous with your time and for offering warmth and reassurance when it was needed.

Iain, thank you for coaching me to think critically and for nurturing my growth as a scientific thinker. Your knowledge of so many things is incredible, and yet you make me, and your other students, feel like the expert in the room. Thank you for all of the time and energy you have invested in me, and for the patience you have shown me as I find my way to the end of this chapter.

To the incredible team at the EDU, past and present: it has been a joy to have shared the last six years surrounded by so many supportive, creative, and stimulating people. To Millie, Katie, Lauren, Mariana, Bethan, Rachel, and Daniela, your friendship, compassion, and flare are such a gift. Thank you for supporting me through the highs and lows of this journey. I could not have asked for better cheerleaders. To Lucy, thank you for being generous with your knowledge and for your support navigating the bumpy COVID ride. We were in this together, and I'm so proud of what we have both achieved against all odds. To Luiza and Gemma, thank you for sharing your tDCS expertise, and for going above and beyond to help me get this project off the ground. Finally, to Amelia, Basak, Lucy, Molly, and Manar, thank you for your generous support at the final sprint. Your readiness to come to my aid was a wonderful reminder of the incredible colleagues and friends I have at the EDU.

To my family – Mum, Dad and Liv, thank you for always encouraging me to take risks and to challenge myself. I could never have done this without your unwavering love, support, and faith in me. Even though you're are miles away, I can feel your warmth and I can hear you cheering me on. Likewise, to Sarah, I can't express how grateful I am for your enduring friendship, even when the distance between us is vast.

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Finally, to the participants who took part in this study. The knowledge gained through your participation has helped us to better understand this new option for treatment in binge eating disorder and paved the way for future studies. I cannot thank you enough.

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Table of contents

List of abbreviations

Abbreviations are reintroduced in each chapter. In alphabetical order:

ABMT	Attention bias modification training
ADHD	Attention deficit hyperactivity disorder
AL/CR	Anode left/cathode right
AN	Anorexia nervosa
AR/CL	Anode right/cathode left
AUC	Area under the curve
BAME	Black, Asian, and ethnic minority
BIS-11	Barrett Impulsiveness Scale
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
BOLD	Blood oxygen level dependent
CBM	Cognitive bias modification
CBT	Cognitive behaviour therapy
CI	Confidence Interval
CIA	Clinical Impairment Assessment
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
DASS-21	Depression, Anxiety, Stress Scale
DBS	Deep brain stimulation
DERS	Difficulties in Emotion Regulation Scale
DLPFC	Dorsolateral prefrontal cortex
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5^{th} Ed.)
ECT	Electroconvulsive therapy
ED	Eating disorder
EDDS	Eating Disorder Diagnostic Screen
EDE-Q	Eating Disorder Examination Questionnaire
EDNOS	Eating disorder not otherwise specified
ECG	Electrocardiogram
EEG	Electroencephalogram
FCT-Tr	Food Craving Questionnaire – Trait Version

GABA	Gamma-aminobutyric acid
GP	General practitioner
GWAS	Genome-wide association study
HC	Healthy control
ICD	International Statistical Classification of Diseases and Related Health Problems
IoPPN	Institute of Psychiatry, Psychology and Neuroscience
KCL	King's College London
Kg	Kilogram
LDX	Lisdexamphetamine
M	Mean
mA	Milliamps
MDD	Major depressive disorder
(f)MRI	(Functional) Magnetic resonance imaging
Ms	milliseconds
mV	millivolts
N	Number of observations
NHS	National health Service
NIBS	Non-invasive brain stimulation
NICE	National institute for Health and Care Excellence
PET	Positron emission topography
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
RCT	Randomise controlled trial
RTs	Reaction Times
SSRI	Selective serotonin reuptake inhibitor
TBS	Theta burst stimulation
TAU	Treatment as usual
(r)TMS	(Repetitive) Transcranial magnetic stimulation
TBS	Theta burst stimulation
TDCS	Transcranial direct current stimulation
VAS	Visual Analogue Scale
WHO	World Health Organisation
WL	Waiting list

List of tables

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Dissemination of research

Publications incorporated into thesis

Chapter 4: Flynn, M., Campbell, I., & Schmidt, U. (2022). Does concurrent self-administered transcranial direct current stimulation and attention bias modification training improve symptoms of binge eating disorder? Protocol for the TANDEM feasibility randomized controlled trial. *Frontiers in Psychiatry*, 13. doi:10.3389/fpsyt.2022.949246

Publications completed during this PhD but not included in thesis

Allen, K., Mountford, V., Elwyn, R., Flynn, M., Fursland, A., Obeid, N., Partida, G., Richards, K., Schmidt, U., Serpell., L., Silverstein, S., Wade, T. (2022). A framework for conceptualising early intervention for eating disorders. *European Eating Disorders Review,* Online Version of Record before inclusion in an Issue. Doi: *10.1002/erv.2959*

Gallop, L., Flynn, M., Campbell, I., & Schmidt, U. (2022). Neuromodulation and eating disorders. *Current Psychiatry Reports,* 24(1), 61-69. doi: 10.1007/s11920-022-01321-8

Flynn, M., Austin, A., Lang, K., Allen, K., Bassi, R., Brady, G., Brown, A., Connan, C., Franklin-Smith, M., Glennon, D., Grant, N., Jones, W. R., Kali, K., Koskina, A., Mahony, K., Mountford, V., Nunes, N., Schelhase, M., Serpell., L., & Schmidt, U. (2021). Assessing the impact of First Episode Rapid Early Intervention for Eating Disorders on duration of untreated eating disorder: A multi-centre quasi-experimental study. *European Eating Disorders Review*, 29(3), 458-471. doi: 10.1002/erv.2797

Austin, A., Flynn, M., Richards, K. L., Sharpe, H., Allen, K., Mountford, V. A., Glennon, D., Grant, N., Brown, A., Mahony, K., Serpell, L., Brady, G., Nunes, N., Connan, F., Franklin-Smith, M., Schelhase, M., Jones, W., R., Breen, G., & Schmidt, U. Early weight gain trajectories in first episode anorexia: Predictors of outcome for emerging adults in outpatient treatment. *Journal of Eating Disorders*, 14(9), 112. doi: 10.1186/s40337-021-00448-y

Austin, A., Flynn, M., Shearer, J., Long, M., Allen, K., Mountford, V. A., Glennon, D., Grant, N., Brown, A., Franklin-Smith, M., Schelhase, M., Jones, W. R., Brady, G., Nunes, N., Connan, F., Mahony, K., Serpell, L., & Schmidt, U. (2021). The First Episode Rapid Early Intervention for Eating Disorders-Upscaled study: Clinical outcomes. *Early Intervention in Psychiatry*, 1– 9. doi: 10.1111/eip.13139

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Richards, K. L., Flynn, M., Austin, A., Lang, K., Allen, K. L., Bassi, R., Brady, G., Brown, A., Connan, F., Franklin-Smith, M., Glennon, D., Grant, N., Jones, W. J., Kali, K., Koskina, A., Mahony, K., Mountford, V. A., Nunes, N., Schelhase, M, Serpell, L., & Schmidt, U. (2021). Assessing implementation fidelity in the First Episode Rapid Early Intervention for Eating Disorders service model. *BJPsych Open*, 7(3). doi: 10.1192/bjo.2021.51

Austin, A., Potterton, R., Flynn, M., Richards, K., Allen, K., Grant, N., Glennon, D., Mountford, V. A., Franklin-Smith, M., Schelhase, M., Jones, W. R., Serpell, L., Mahony, K., Brady, G., Nunes, N., Kali, K., Connan, F., & Schmidt, U. (2021). Exploring the use of individualised patient-reported outcome measures in eating disorders: Validation of the Psychological Outcome Profiles. *European Eating Disorders Review*, 29(2), 281-291. doi: 10.1002/erv.2819

Potterton, R., Austin, A., Flynn, M., Allen, K., Lawrence, V., Mountford, V., Glennon, D., Grant, N., Brown, A., Franklin-Smith, M., Schelhase, M., Jones, W. R., Brady, G., Nunes, N., Connan, F., Mahony, K., Serpell, L., & Schmidt, U. (2021). “I’m truly free from my eating disorder”: Emerging adults’ experiences of FREED, an early intervention service model and care pathway for eating disorders. *Journal of Eating Disorders*, 9(1), 1-14. doi: 10.1186/s40337-020-00354-9

Conference and research presentations associated with thesis

Conference presentations:

Flynn, M., Campbell, I., & Schmidt, U. (2022). An intervention with spark: Clinical and feasibility outcomes from the TANDEM trial of concurrent transcranial direct current stimulation and attention bias modification training in binge eating disorder. Oral presentation at the Academy for Eating Disorders International Conference on Eating Disorders, online.

PhD showcases:

Flynn, M (2019). Neuromodulation for Binge Eating Disorder. Oral presentation at the Biomedical Research Centre (BRC) Obesity, Lifestyle and Learning from Extreme Phenotypes (OBELIX) Theme Showcase.

External Workshops and Meetings:

Flynn, M, Gallop, L., & Schmidt, U. (2022). Brain stimulation for eating disorders. Webinar presentation for Eating Disorder Families Australia.

Flynn, M, Gallop, L., & Schmidt, U. (2022). Neuromodulation for eating disorders. Webinar presentation for Academy for Eating Disorders.

Flynn, M, Gallop, L., & Schmidt, U. (2021, 2022). Brain stimulation for eating disorders. Webinar presentation for Maudsley Learning.

Internal meetings:

The research included within this thesis has been presented at departmental meetings at the Institute of Psychiatry, Psychology & Neuroscience, King's College London. Presentation titles included: (1) "Taking tDCS into the home: A protocol for a randomised controlled feasibility trial in binge eating disorder" and (2) "Preliminary findings from the TANDEM trial of at-home tDCS with attention bias modification training in Binge Eating Disorder".

Declaration of the candidate's role

Chapter 1: General introduction

The candidate (Michaela Flynn) conceptualised and drafted the chapter. Professor Ulrike Schmidt and Professor Iain Campbell provided constructive feedback.

Chapter 2: The effect of non-invasive brain stimulation targeting the DLPFC on emotional attention bias: A systematic review and meta-analysis

The review was conceived by the candidate, Professor Ulrike Schmidt, and Professor Iain Campbell. The literature search was conducted by the candidate and Amelia Hemmings. Data extraction was conducted by the candidate and Dr Bethan Dalton and checked by Amelia Hemmings and Dr Lauren Robinson. The quality assessment for included papers was completed by the candidate, Basak Ince, Lucy Hyam, Mariana de Padua-Lopes. The candidate completed the data synthesis and meta-analysis with statistical supervision by Dr Lauren Robinson. The candidate authored the chapter with constructive feedback from her supervisors.

Chapter 3: Chapter 3. Food-Related Attention Bias in Binge Eating Disorder and Obesity

The candidate designed the study with her supervisors, Professor Ulrike Schmidt and Professor Iain Campbell. The candidate obtained ethical approval from the King's College London Research Ethics Committee and the National Health Service (NHS) Research Ethics Committee and Health Research Authority. Recruitment and data collection were performed by the candidate (main contributor), Maaike Rae Boek and Katie Patterson. Data entry and statistical analyses were performed by the candidate. The candidate authored the chapter and received constructive feedback from her supervisors.

Chapter 4: Does concurrent self-administered transcranial direct current stimulation (tDCS) and attention bias modification training improve symptoms of binge eating disorder?

The TANDEM study was conceptualised and designed by the candidate with her supervisors, Professor Ulrike Schmidt and Professor Iain Campbell. The candidate drafted the chapter and received constructive feedback from her supervisors,

Professor Ulrike Schmidt and Professor Iain Campbell, and from peer reviewers from *Frontiers in Psychiatry*.

Chapter 5: An intervention with spark: Clinical and feasibility outcomes from the TANDEM trial of concurrent transcranial direct current stimulation and attention bias modification training in binge eating disorder.

The study was conceptualised and designed by the candidate (Michaela Flynn), Professor Ulrike Schmidt and Professor Iain Campbell. The candidate obtained ethical approval from the NHS Research Ethics Committee and the Health Research Authority. The candidate performed all aspects of recruitment, delivery of the trial interventions, data collection, data entry, and data analysis. The candidate drafted the chapter with constructive feedback from her supervisors, Professor Ulrike Schmidt and Professor Iain Campbell.

Chapter 6: Examining the effect of at-home tDCS with attention bias modification training on attention bias towards food: Outcomes from a randomised sham-controlled feasibility trial in binge eating disorder

The study was conceptualised and designed by the candidate (Michaela Flynn), Professor Ulrike Schmidt and Professor Iain Campbell. The candidate obtained ethical approval from the NHS Research Ethics Committee and the Health Research Authority. The candidate performed all aspects of recruitment, delivery of the trial interventions, data collection, data entry, and data analysis. The candidate drafted the chapter with constructive feedback from her supervisors, Professor Ulrike Schmidt and Professor Iain Campbell.

Chapter 7: General overview

The candidate conceptualised and drafted the chapter. Professor Ulrike Schmidt and Professor Iain Campbell reviewed the chapter and provided constructive feedback.

Chapter 1. General introduction

Author contributions: The candidate (Michaela Flynn) conceptualised and drafted the chapter. Professor Ulrike Schmidt and Professor Iain Campbell provided constructive feedback.

1.1 Binge eating disorder: An overview

Binge eating disorder (BED) was first described by psychiatrist Albert Stunkard in 1959 in his paper titled, "Eating Patterns and Obesity". Here, he described an eating pattern which has "an orgiastic quality" during which "enormous amounts of food may be consumed in relatively short periods…during periods of life stress…with no particular periodicity" (Stunkard, 1959). As studies of this unusual eating behaviour increased, so did potential names to describe the phenomenon. Psychiatrists suggested terms like, "Stuffing Syndrome," "Thin/Fat Syndrome," "Hyperorexia," and "Dietary Chaos Syndrome." Eventually, the term "binge eating" became the accepted nomenclature and, in 1980, the term was first noted in the third edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-III; American Psychiatric Association, 1980) as a feature of another eating disorder (ED), bulimia nervosa (BN). Later, in 1987 when the DSM-III was revised (DSM-III-r; American Psychiatric Association, 1987), a third category of ED was described: Eating Disorder Not Otherwise Specified (EDNOS). This category, which was designed to recognise individuals with clinically significant disordered eating who did not meet diagnostic criteria for anorexia nervosa (AN) or BN, became the diagnostic 'home' for people with BED for the following 25 years.

In the years that followed, EDNOS became the most common ED, with as many as half of all individuals diagnosed with an ED receiving this diagnosis. Not surprisingly, clinicians and academics in the field expressed concern about the utility of a classification system which saw such a high proportion of patients captured by a 'residual' diagnostic category (e.g., Fairburn et al., 1993, and Spitzer et al, 1993). In response, in 1994, BED was re-classified as a provisional diagnosis within EDNOS which could be applied for research purposes (DSM-IV; American Psychiatric Association, 1994), and for the first time, criteria for diagnosis were described. This facilitated more numerous and more rigorous research into BED which, in time, provided the empirical evidence needed to demonstrate that recognition of BED as a full syndrome ED is clinically and academically advantageous. Accordingly, BED was finally described as a full-syndrome ED in the fifth edition of the DSM published in 2013 (DSM-5; American Psychiatric Association, 2013) and in the 11th edition of the International Classification of Diseases published in 2019 (ICD-11; World Health Organisation, 2019).

The protracted period during which BED lacked formal recognition and definition hampered efforts to investigate this population and contributed to BEDs position as the "lesser known" and more steeply stigmatised ED. Indeed, a recent review painted a bleak picture of public and healthcare practitioner knowledge about BED, and their attitudes and beliefs about those living with the disorder (Reas, 2017). Here, it was reported that the public perceived BED as less impairing, less severe, and "easier-to-treat" than other EDs, and that both public and healthcare practitioner attitudes and beliefs about BED reflected perceived blameworthiness and lack of self-discipline (Reas, 2017). Although this is disheartening, in the ~10 years since BED's inclusion in the DSM-5, there has been marked improvement in BED recognition among healthcare professionals (Reas, 2017) and the number of studies focusing on BED has increased exponentially: according to PubMed®, only ~1,200 studies of BED had been published prior to the DSM-5 publication in 2013. Since then, more than 1,800 new studies of BED have been published.[1]

1.1.1 Diagnosis and clinical characteristics

BED is characterised by regular episodes of objective binge eating during which an individual ingests a large amount of food over a discrete period of time whilst experiencing loss of control over eating behaviour (Giel, Bulik, et al., 2022). According to the DSM-5, to qualify for a BED diagnosis these episodes must occur at least once per week for at least 3 months, and they must be accompanied by distress. These episodes must also be associated with at least three of the following five characteristics: eating much more rapidly than normal, eating until feeling uncomfortably full, eating despite not feeling physically hungry, eating alone because of embarrassment about the amount of food being consumed, and/or negative feelings after overeating (American Psychiatric Association, 2013). Similar criteria for diagnosis were described in the ICD-11 however, here a more relaxed definition of binge eating has been applied. While the DSM-5 requires that episodes of binge eating involve the consumption of an *objectively* large amount of food, in the ICD-11 consumption of a *subjectively* large amount of food is sufficient for diagnosis (World Health Organisation, 2019). During episodes of objective binge

[1] The DSM-5 was released on the 13th of May 2013. The PubMed® database includes 1238 publication using the term "binge eating disorder" in the title or abstract prior to this date. Between the 14/05/13 and 01/09/22, 1830 publications used the term "binge eating disorder" in the title or abstract.

eating, people with BED commonly consume high-calorie palatable foods including breads/pasta, sweets, high fat meat items, and salty snacks (Allison & Timmerman, 2007).

Binge eating is a feature of BED, BN, and some presentations of AN. However, the regular use of inappropriate compensatory behaviours to prevent weight gain (e.g., self-induced vomiting, laxative misuse, or severe caloric restriction), which characterises BN and AN binge/purge subtype, is not a feature of BED (World Health Organisation, 2019). Similarly, unlike AN and BN, body image disturbances (e.g., overvaluation of weight and shape) are not currently required for BED diagnosis (World Health Organisation, 2019). However, ~50% of individuals with BED report clinically significant overvaluation of weight and shape, and outcomes from treatment are poorer for these individuals (Coffino et al., 2019a; Grilo et al., 2008; Grilo et al., 2019; Grilo et al., 2013).

The DSM-5 also provides criteria for full and partial remission. Partial remission of BED is fulfilled if, after full criteria were previously met, binge eating frequency is reduced to less than once per week for a sustained period of time. Full remission is achieved when an individual no longer meets any of the DSM-5 criteria for BED and has done so for a sustained period of time (American Psychiatric Association, 2013). However, the duration of this "sustained period of time" is not specified so clinical judgement is required.

1.1.2 Help-seeking behaviour

It is reported that only ~50% of affected persons with BED ever seek help for their ED, and that help-seeking rates are even lower in men and in ethnic minority groups (Coffino et al., 2019b). Prominent barriers to help-seeking include stigma and shame, lack of insight into the severity of the illness, low motivation to change, negative attitudes toward seeking help, lack of encouragement from others to seek help, lack of knowledge about help-seeking options, and practical barriers (e.g., proximity to/cost of care; Ali et al., 2017; Ali et al., 2020). Indeed, individuals with BED typically seek help for weight management in the first instance, and many do not recognise or disclose that their behaviour is consistent with an ED (Coffino et al., 2019b). Similarly, healthcare professionals are often unfamiliar with the BED diagnosis, and they frequently hold negative attitudes and beliefs about people with

BED (Reas, 2017). These contribute to failures detecting the disorder and hamper help seeking efforts.

1.1.3 Epidemiology

1.1.3.1 Prevalence

Given BED's relatively recent addition to international disease classification systems, knowledge of epidemiology is still emerging. Clinical and community-based studies, most of which have been conducted in high-income countries across North America, Europe, and Oceania, suggest that BED is common in the general population (Giel, Bulik, et al., 2022). Indeed, BED is the most common full-syndrome ED. Across 94 studies, the most common ED was other specified feeding or eating disorder (OFSED)/EDNOS with lifetime and point prevalence of 4.3% and 10.1% for females and 3.6% and 0.9% for males. This was followed by BED with lifetime and point prevalence of 2.8% and 2.3% for females, and 1% and 0.3% for males (Galmiche et al., 2019). Of note, expert reviews of worldwide ED epidemiology have called for larger, more rigorous studies to produce a better understanding of the prevalence and distribution of EDs (Hoek, 2016). This is especially needed because of the changes to criteria for ED diagnosis outlined in the DSM-5 (American Psychiatric Association, 2013), including the recognition of BED as a clinical diagnosis and the relaxation of BED diagnostic criteria relative to those described for use in research in the DSM-IV (American Psychiatric Association, 1994). Moreover, very few of the available epidemiological studies distinguished males from females, many only included females, and data relating to low- and middle-income countries (Udo & Grilo, 2018), ethnic minority groups (Rodgers et al., 2018) and gender-diverse populations (Gordon, et al., 2021) are lacking.

1.1.3.2 Illness course

BED has a relatively late age of onset and protracted illness course. Although symptoms of BED can begin as young as age 8 years (Tanofsky-Kraff et al., 2005), the median age of onset for BED is ~20 years (Kessler et al., 2013; Solmi et al., 2022). Where there is no prior history of ED, BED onset is rare after age 30 years (Solmi et al., 2022). Most long-term studies have suggested that BED is often long-standing, with a mean illness duration of 14-16 years reported in adults (Agh et al., 2015; Keski-Rahkonen, 2021; Udo & Grilo, 2018). Studies in adolescents and young

adults report a much shorter mean duration of BED. For example, in a longitudinal study of ~9,000 adolescent women in North America, only 10.8% of participants who met diagnostic criteria for BED at baseline continued to do so at 2-year follow-up (Glazer et al., 2019). Similarly, in a Finnish study of young adults (age < 25 years), the mean duration of BED was 4 years, and 40% of participants achieved full recovery within 5 years of BED onset (Silen et al., 2021). This may indicate that BED is fundamentally different in youth, however, more likely it highlights the importance of early detection and intervention in achieving remission.

Fluctuations in ED presentations are frequently reported in the literature, although this appears to be less common in BED, as opposed to other EDs (Udo & Grilo, 2018). In a large Swedish population study, researchers mapped transition patterns for 9,622 individuals who were seen for an ED at least twice in the 14-year period between 1999 and 2013 (Schaumberg et al., 2019). They observed that, in general, transitions across full-syndrome EDs were rare, and that transition to remission (33%) or retention of BED diagnoses (42%) was the most common pattern for those first diagnosed with BED in this sample. Where shifting did occur, the likelihood of remission decreased, indicating that diagnostic instability may indicate greater BED severity and poor prognosis (Schaumberg et al., 2019).

1.1.3.3 Medical comorbidity

BED is associated with a wide range of significant and disabling medical comorbidities (Giel, Bulik, et al., 2022). In a recent study of more than 36,000 adults in the United States of America, past-year health conditions commonly co-occurring with BED (with or without obesity) included hypertension (31%), various heart conditions (17%), arthritis (24%), elevated cholesterol (27%) and triglycerides (15%), diabetes mellitus (14%), and sleep problems (29%) (Udo & Grilo, 2019).

Due to high caloric consumption during episodes of objective binge eating, BED and obesity are highly comorbid, and ensuing obesity-related medical complications are common (Wassenaar et al., 2019). In a recent study of a nationally representative sample of adults in the United States (n = 35,306), participants with a lifetime diagnosis of BED (n = 318) were 2.09 times more likely than participants with no history of ED to report a current BMI between 30.0 and 39.9 kg/m^2, and 4.61 times more likely to report a BMI ≥40 kg/m^2 (Udo & Grilo, 2018). Similarly, those who

met criteria for BED within the previous 12-months were 1.86 times more likely to report current BMI between 30 and 39.9 kg/m^2, and 1.95 times more likely to report BMI ≥40 kg/m^2 (Udo & Grilo, 2018). Accordingly, individuals with BED are overrepresented among bariatric surgery candidates (Wassenaar et al., 2019). For example, in a systematic review of maladaptive eating behaviours among bariatric surgery candidates, it was reported that up to 49% of individuals in pre-operative samples met full criteria for BED, and that 66% reported at least one episode of binge eating per week (Williams et al., 2017). Post-surgery, BED is associated with poorer surgical outcomes, less weight loss, more weight re-gain, and increased need for surgical revision (Conceição et al., 2015).

Rates of metabolic syndrome (i.e., the clustering of a number of obesity-related medical conditions including abdominal obesity, hyperglycaemia, hyperlipidaemia, and hypertension) are also elevated in BED (Wassenaar et al., 2019), although the criteria used to diagnose metabolic syndrome vary across studies. Those with metabolic syndrome are at a 1-2-fold increased risk of cardiovascular disease (Mottillo et al., 2010; Guembe et al., 2020) and Alzheimer's dementia (Kim et al., 2021), as well as a 2-5-fold increased risk for type 2 diabetes mellitus (Shin et al., 2013). Indeed, it has been suggested that risk for development of type 2 diabetes mellitus is up to 13 times greater in BED, relative to those with healthy weight (Raevuori et al., 2015), and that up to 25% of patients with type 2 diabetes may have BED (Hudson et al., 2010). Relatedly, metabolic and inflammatory markers associated with increased morbidity and mortality, such as erythrocyte sedimentation rate, high-sensitive C-reactive protein, and white blood cell count, are also elevated in individuals with obesity who meet criteria for BED, relative to controls with obesity (and not BED) and healthy-weight (Succurro et al., 2015). Given high levels of obesity, insulin resistance, and metabolic syndrome, people with BED may also be at greater risk for developing non-alcoholic fatty liver disease. A pilot study in adults with non-alcoholic fatty liver disease (n = 95) reported that 23.1% of participants scored highly on the Binge Eating Scale (Gormally et al., 1982), suggesting probable BED (Zhang et al., 2017).

Type 1 diabetes mellitus and other autoimmune disorders, such as Chron's disease and autoimmune thyroiditis, may also be more common in patients with BED, although these are less well documented in the literature (Raevuori et al., 2014;

Wassenaar et al., 2019). Disinhibited eating has been reported among individuals with type 1 diabetes, and up to 27% of those with type 1 diabetes who engage in disinhibited eating also report insulin misuse for weight control (Colton et al., 2015; Merwin et al., 2014). Less is known about individuals with type 1 diabetes who experience disinhibited eating but do not employ maladaptive weight control behaviours, although they appear to be numerous, and it is possible that a large portion may meet criteria for BED (Takii et al., 2002; Wassenaar et al., 2019).

Gastrointestinal symptoms, including dysphagia, acid reflux, bloating, abdominal pain, diarrhoea, constipation, and lower gastrointestinal urgency, are common in obesity and more so in BED (Cremonini et al., 2009). In fact, BED seems to be associated with both upper and lower gastrointestinal symptoms, independent of the level of obesity (Cremonini et al., 2009). Risk for nutritional deficiency, particularly for vitamins A, C, D3 and calcium, is also increased (Wassenaar et al., 2019). Additionally, respiratory, musculoskeletal, and reproductive health problems (e.g., urinary incontinence, polycystic ovarian syndrome, and infertility) are significantly increased in patients with BED compared with the general population (Wassenaar et al., 2019).

1.1.3.4 Psychiatric comorbidity

BED often co-occurs with other mental health conditions. A recent study of BED prevalence and correlates which was conducted in a large nationally representative sample (n =35,306) reported that 94% of individuals with BED with or without obesity met diagnostic criteria for at least one additional psychiatric disorder and 23% had attempted to die by suicide (Udo & Grilo, 2019). Common psychiatric comorbidities among participants with BED with and without obesity included lifetime mood disorders (70%), post-traumatic stress disorder (32%) and anxiety disorders (16%), and multiple psychiatric comorbidities were common (Udo & Grilo, 2019). Indeed, individuals with BED with and without obesity met criteria for a significantly greater number of lifetime psychiatric diagnoses than those with AN, after adjusting for sociodemographic variables (mean lifetime comorbid psychiatric diagnoses: BED with and without obesity = 2.3, AN = 1.7) (Udo & Grilo, 2019). These findings are consistent with those reported ~12 years earlier using data from the National Comorbidity Survey Replication which included 2980 adults with EDs (Hudson et al., 2007). Here, almost 50% of respondents with BED with and without

obesity met diagnostic criteria for three or more psychiatric comorbidities at the time of assessment (Hudson et al., 2007). Other common comorbidities include addiction disorders such as substance use/abuse [e.g., 22.0% of participants with obesity and BED in Grilo et al. (2013)], gambling problems [e.g., 5.7% of participants with BED and without obesity in Jiménez-Murcia et al. (2013), and 18.7% of participants with obesity and BED in Yip et al. (2011)], and compulsive buying [e.g., 7.4% of participants with BED with and without obesity in Müller and Mitchell (2014), and 18.5% of participants with obesity and BED in Fernández-Aranda et al. (2019)]. Attention-deficit–hyperactivity disorder (ADHD) and BED also commonly co-occur ((Udo & Grilo, 2019).

Psychiatric comorbidity is associated with more severe BED pathology and poorer response to treatment, regardless of the evidence-based treatment used (Giel, Bulik, et al., 2022; Lydecker & Grilo, 2021). For example, in a recent study of 636 adults with BED, generalised psychiatric comorbidity and current mood disorder comorbidity predicted more frequent episodes of binge eating and higher global ED psychopathology at both pre- and post-treatment timepoints, compared with BED patients without psychiatric comorbidity (Lydecker & Grilo, 2021). Similarly, patients with a comorbid mood disorder were less likely to experience remission from binge eating at end-of-treatment. However, psychiatric comorbidity neither predicted nor moderated weight loss in patients with BED (Lydecker & Grilo, 2021).

1.1.3.5 Burden of disease

Given the high prevalence of BED and the high rates of BED comorbidity, the economic and quality of life burden associated with BED is substantial (Le & Mihalopoulos, 2021; Santomauro et al., 2021; Streatfeild et al., 2021). In a recent examination of the social and economic costs of EDs in the United States, Streatfield et al. (2021) estimated that in the fiscal year of 2018-2019, EDs were associated with a tangible cost (i.e., health system costs and costs associated with productivity loss) of 64.7 billion USD and an intangible cost (i.e., costs associated with loss of wellbeing) of 326.5 billion USD. Here, BED accounted for 30% of tangible costs (19.4 billion USD) and nearly 40% of intangible costs (128.8 billion USD). Similarly, in an extension to the Global Burden of Diseases, Injuries, and Risk Factors Study, it was reported that during 2019 BED accounted for 800,000 disability-adjusted life years (i.e., lost years of healthy life due to either mortality or

disability; Santomauro et al, 2021).

1.2 Aetiology of BED

Although our knowledge of BED aetiology is still emerging, it is widely accepted that a range of psychological, environmental, and genetic factors, and the interactions between them, contribute to the development and maintenance of BED.

1.2.1 Psychological risk factors

Empirical evidence indicates that a range of psychological and behavioural factors may contribute to the development of BED (Agüera et al., 2021; Davis et al., 2020; Micali et al., 2017). First, childhood loss-of-control eating (Tanofsky-Kraff et al., 2005; Tanofsky-Kraff et al., 2011) and eating in the absence of hunger (Balantekin et al., 2017) have been shown to predict BED onset during adolescence. For example, in a prospective longitudinal study of 195 children aged 6 to 13 years, it was found that those who reported having ever experienced loss of control eating at baseline were significantly more likely to develop partial or full-syndrome BED according to DSM-IV criteria by 5-year follow-up than children who reported no history of loss of control eating at baseline (Tanofsky-Kraff et al., 2011). Similarly, dieting behaviour during adolescence is a significant risk factor for later binge eating behaviour (e.g., Robinson et al., 2020).

Second, while BED, by definition, often entails intense feelings of depressed mood following binge eating episodes (American Psychiatric Association, 2013), negative affect has been implicated in both the development and maintenance of the disorder. For example, prospective longitudinal studies report that unhappiness during childhood predicts future BED onset (Micali et al., 2017). Similarly, depressive symptoms in adolescence and young adulthood have also been shown to predict the development of BED during adulthood (Goldschmidt et al., 2016; Stice et al., 2017; Stice et al., 2002). Among individuals with BED, low affect has also been shown to increase the likelihood of future episodes of binge eating (Cardi et al., 2015; Haedt-Matt & Keel, 2011; Zaider et al., 2002), and is therefore implicated in maintenance models of BED (e.g., Leehr et al.,2015).

Third, generalised anxiety, social anxiety, and elevated stress are also predictive risk factors for BED (Stice et al., 2017). In a prospective longitudinal study including 45 women with a lifetime history of BN or BED and 1,515 control women, greater

levels of perceived stress were found to predate the onset of binge eating across BN and BED (Striegel-Moore et al., 2007). A longitudinal study of 201 American adolescents similarly found that greater anxiety was associated with later onset of BED (Zaider et al., 2002). Social phobia and conduct disorder during adolescence have also been reported to be a significant predictor of future binge eating behaviour in general (Robinson et al., 2020). Relatedly, low self-esteem, negative body image and maladaptive internalised beliefs about thinness may also contribute to the development of BED (Stice & Desjardins, 2018). For example, in a study of 1,272 individuals with EDs, body dissatisfaction, perceived pressure for thinness, internalisation of the 'thin-ideal', and strong beliefs about social and psychological benefits of thinness were all found to be specific predictors of later BED onset (Stice et al., 2017). Maladaptive cognitions relating to body image, including low interoceptive awareness, elevated body dissatisfaction and body disinvestment, have also been implicated (Cella et al., 2021, 2022). This relationship between negative body image and binge eating behaviour may be moderated by low self-esteem (Puttevils et al., 2019). Indeed, low self-esteem is a well-established non-specific risk factor for EDs which is known to interact with risk factors for BED (Sehm & Warschburger, 2015).

Finally, a number of personality traits have been identified as risk factors for BED. High levels of neuroticism, low levels of agreeableness, and elevated impulsivity are significant predictors of future binge eating behaviour (Robinson et al., 2020; Stice et al., 2017; Zhang et al., 2021). For example, in a longitudinal population-based study of 1,623 adolescents, high levels of neuroticism, elevated impulsivity, and low levels of agreeableness at 14 years of age were associated with binge eating behaviour at age 16 and 19 (Robinson et al., 2020). The combination of high impulsivity and neuroticism has been conceptualised as *negative urgency*: the tendency to engage in rash actions and risky behaviours (i.e., impulsivity) when experiencing strong negative emotions (i.e., neuroticism). Negative urgency is detectable from childhood and has been shown to prospectively predict high school binge eating (Davis & Smith, 2018), which in turn predicts BED in adulthood (Goldschmidt et al., 2016).

1.2.2 Environmental risk factors

Environmental factors related to poor family functioning, weight and body shape-based teasing, and childhood trauma have all been found to increase risk of BED

later in life (Keski-Rahkonen, 2021). For example, a longitudinal study of 1,043 UK women found that low maternal warmth and an oppressive parental relationship significantly predicted the future onset of BED (Micali et al., 2017). Similarly, parental depression (Fairburn et al., 1998), substance abuse (Boswell & Grilo, 2021), anxiety (Striegel-Moore et al., 2007), and disordered eating behaviours (Manwaring et al., 2006) also elevate risk of BED. Weight and shape related stigmatisation, both within and outside of the family, also increase risk for BED (Almeida et al., 2011; Fairburn et al., 1998; Goncalves et al., 2014; Pike et al., 2006), as does non-weight and shape-based bullying in childhood, as demonstrated by longitudinal and retrospective interview studies (Copeland et al., 2015; Striegel-Moore et al., 2002).

Childhood experiences of trauma or abuse are also linked to elevated BED risk. A systematic review of studies examining the effect of abuse during childhood and adolescence on the development of obesity and BED reported that, based on 10 studies conducted in BED, there is strong evidence to support the relationship between trauma and the development of BED in adulthood (Palmisano et al., 2016). This association between adulthood BED and trauma was strongest when the abuse started at an early age or when the abuse was more severe (Palmisano et al., 2016). These findings are consistent with those reported in a large meta-analysis investigating the effect of abuse on general ED risk (Caslini et al., 2016). However, it should be noted that almost all studies linking childhood abuse to BED use retrospective study designs and, therefore, findings should be interpreted with caution given the possibility of recall bias (Caslini et al., 2016). Future prospective longitudinal studies will help to clarify aetiological pathways from abuse to BED, as well as influential protective factors.

Mixed findings have been reported with regards to the effect of socioeconomic status on BED and binge eating behaviour; on the one hand, one cross-sectional study of 475 people in the Detroit metropolitan area found that lower income was associated with increased frequency of binge eating in women, but not men (Reagan & Hersch, 2005). On the other hand, larger Australian studies of 4,200 and 6,041 people, respectively, found no association between household income and binge eating (Hay, 1998; Mulders-Jones et al., 2017). Additionally, a recent study of 35,306 American adults also failed to find an association between income level and risk for BED (Udo & Grilo, 2018). However, emerging evidence suggests that household food-

insecurity, a direct by-product of low socioeconomic status, is a specific risk factor for developing BED (Becker, et al., 2019; Bruening, et al., 2012; Rasmusson, et al., 2018). As such, more numerous and more representative data are needed to facilitate a nuanced understanding of socioeconomic risk factors for BED.

Finally, while female sex is a significant risk factor for developing AN or BN, BED risk appears to be comparable among men and women. Although few studies have examined ED risk in transgender and gender non-binary populations, disordered eating behaviours in general are estimated to be 2-4 times more likely in transgender and non-binary people (Gordon et al., 2021; Uniacke, Glasofer, Devlin, Bockting, & Attia, 2021). Similarly, sexual minority groups are reported to be disproportionately affected by EDs, including BED (Kamody et al., 2020). Findings relating to ethnic and cultural differences in ED diagnoses and risk factors have been mixed. Overall, most findings appear to suggest that ED affect ethnic minorities as much as they do White populations, and that there are more overlapping risk factors shared among various ethnic groups than differences (Cheng et al., 2019; Rodgers et al., 2018). Where differences are reported, they largely relate to the extent to which different ethnic groups value and celebrate thinness (i.e., the 'thin-ideal'). For example, several studies found that Asian American women report significantly higher thin-ideal internalisation than both White and African American women, and that African American women reported lower levels of body dissatisfaction than White and Asian American women (Cheng et al., 2019; Herbozo et al., 2017; Martin & Racine, 2017; Rubin et al., 2003). Importantly, stigma and stereotypes associated with gender, ethnicity, mental health status, weight, age, and various disadvantaged positions, such as disability and lack of resources, may decrease the visibility of BED (Becker, et al., 2003; Puhl & Suh, 2015). As such, these individuals may be at greater risk of undetected BED.

1.2.3 Genetic risk factors

Although genetic factors have been implicated in the aetiology of EDs, studies of molecular genetics in EDs have been limited, and most have focused on AN. Nevertheless, heritability of current BED is estimated to be between 41% and 57%, with somewhat lower estimates of heritability found in twin studies (Bulik et al., 2003; Mitchell et al., 2010; Reichborn-Kjennerud et al., 2004) versus a case-control study (Javaras et al., 2008). Heritability of binge eating behaviour, in general, has

been found to be as high as 70% to 74% (Root et al., 2010).

Most studies of genetic risk factors for BED have focused on candidate genes, and a recent systematic review of 21 such studies reported that 11 single-nucleotide polymorphisms (SNPs) across 9 genes have been associated with BED (Manfredi et al., 2021). These include polymorphisms of the serotonin (5HT) transporter gene (5-HTTLPR), dopamine (D2) receptor/ankyrin gene (Taq1A, A118G, and rs2283265), the COMT gene (Val158Met), the glucocorticoid receptor gene (rs6198), the melanocortin 4 receptor gene (Val103Ile, Ile251Leu), brain-derived neurotrophic factor (rs626), and the ghrelin gene (Leu72Met) (Manfredi et al., 2021). Relating to the serotonergic system, one study which compared participants with BED with obesity (n = 77) with weight-matched controls (n=61) found that both the LL genotype and the L allele of 5-HTTLPR occurred significantly more frequently in BED than in healthy subjects (Monteleone, et al., 2006). The L allele of HTTLPR is associated with increased transcriptional efficiency. As such, the authors hypothesised that subjects homozygous for this allele may express a higher number of 5HT transporter sites at their serotonergic synapses, leading to higher 5HT reuptake activity and reduced 5HT availability in the synaptic cleft. Indeed, low 5HT availability has been shown to be linked to compulsive eating in animal studies (Blundell, 1986). However, the association between 5HT transporter polymorphism and BED with obesity was not replicated in a later study comparing participants with obesity (n = 69, of which 31 also met criteria for BED) and overweight (n = 24) to "healthy weight" controls (n = 62) (Palmeira et al., 2019).

In the dopaminergic system, several studies have reported that the Taq1A polymorphism may have a crucial role in BED aetiology (Davis et al., 2008; Davis et al., 2009; Davis et al., 2012; Palacios et al., 2018). In one study, Taq1A was found to moderate reward sensitivity among individuals with obesity with BED (n = 56), and not weight-matched controls (n=51), who carry the A1 allele (Davis et al., 2008). However, this finding was not replicated in later studies, although these used smaller samples [n = 69, of which 31 also met criteria for BED in Palmeira et al. (2019) and n = 21 with obesity with BED in Rodríguez-López et al. (2021)]. Also relating to the dopaminergic system, Davis et al. (2009) found that SNPs of OPRM1 and DRD2 may distinguish obesity with BED (n = 66) from obesity without BED (n = 70). Specifically, the authors found that a significantly greater number of participants

with obesity had the “loss-of-function” A1 allele of Taq1A than BED counterparts, and that the “gain-of-function” G allele of A118G occurred with greater frequency in the BED group. Similarly, Davis et al. (2012) genotyped functional markers of the D2 receptor in adults with obesity with and without BED (n = 79 and n = 151, respectively). Here, the authors reported that a significantly greater proportion of participants with BED, as opposed to weight-matched controls, were homozygous for the A2 allele of the Taq1A polymorphism. Participants with obesity with BED also had a significantly higher frequency of the T homozygous genotype of the C957T marker and were about half as likely to carry the minor T allele of rs2283265. Taken together, these findings suggest that BED may be associated with genetic polymorphisms linked to enhanced dopamine transmission.

One study has reported that polymorphism of the COMT gene was associated with BED. In their investigation of the Val(108/158)Met polymorphism in participants with obesity with BED (n = 21) and participants with overweight or obesity without BED (n = 23 and n = 25, respectively), Leehr et al. (2016) found that Met/Met homozygous individuals obesity with BED displayed greater deficits in inhibitory control than participants with obesity with BED without the SNP. The authors suggest that this SNP may indicate a specific group in the BED spectrum that is characterised by higher behavioural impulsivity, however, it is important to acknowledge the small sample used in this study. Relatedly, in their study of BDNF gene variation in eating disorders, Ceccarini et al. (2020) found that the rs6265 polymorphism, in the coding region Val66Met of the BDNF gene, showed a strong association with BED (n = 130) and AN (n = 311), as opposed to healthy-weight controls with no history of ED (n = 355). These two conditions have different and specific phenotypic characteristics, suggesting that BDNF could have a crucial role in food intake control and participate in the regulation of both pathways.

Polymorphisms of the glucocorticoid receptor gene and the melanocortin 4 receptor (MC4R), both of which are involved in the regulation of food intake, have also been reported in BED. First, in their study of polymorphisms of the glucocorticoid receptor gene in EDs (n_{AN} =118, n_{BN} = 108, $n_{BED\ with\ or\ without\ obesity}$ = 62), obesity (n = 177) and healthy-weight controls (n = 121), Cellini et al. (2010) found that the rs6198 polymorphism was exclusively associated with binge eating symptoms (i.e., no other association between the different glucocorticoid receptor polymorphisms

and other ED diagnoses were observed). The authors explained their findings by stating that cortisol secretion is an essential component of the stress response, and stress and negative affect are the most cited antecedents of binge eating. Second, two studies have found that a significantly greater proportion of mutation carriers on the MC4R gene present with obesity with binge eating, compared with noncarriers with obesity only: in their study of MC4R gene mutations in obesity with and without BED (n = 47 and n = 247, respectively), Potoczna et al. (2004) found that 100% of participants identified as carriers of the MC4R mutation met criteria for BED (n=19). Similarly, in their study involving 494 participants with severe obesity, 100% of MC4R mutation carriers met criteria for BED (n=25). However, this finding was not replicated in a study by a separate research group (Hebebrand et al., 2004). Finally, in their study of the ghrelin gene mutations in obesity with and without BED (n = 90 and n = 119, respectively), Monteleone et al. (2007) found a significant association between the Leu72Met polymorphism of the ghrelin gene and obesity with BED. Their results seem to suggest that this ghrelin gene variant may confer a moderate but significant risk for developing BED, although they cannot exclude that some unexplored factors could be involved in this association. Indeed, other studies did not find this association between Leu72Met polymorphism of the ghrelin gene and obesity with BED, although non-significant findings may be explained by small sample sizes [n = 38 in Kindler et al. (2011) and n = 31 in Palmeira et al. (2019)].

Although no genome wide association study (GWAS) of BED has been carried out, one study has used polygenic risk scoring (PRS) to explore differences between AN (n = 768), BN (n = 423) and BED with and without obesity (n = 561), relative to healthy-weight controls with no history of disordered eating (n = 15,500) (Hubel et al., 2021). This study found that BED was positively associated with PRS for schizophrenia, major depressive disorder, and ADHD, as well as PRS for several anthropometric traits including waist circumference, hip circumference, overweight, obesity, and childhood obesity. Furthermore, BED was negatively associated with the age at menarche PRS, meaning that increased genetic risk for BED was associated with increased genetic risk for earlier age at menarche. Of interest, this study was the first to show that while genetic risk for other psychiatric disorders was comparable across EDs, the association between genetic risk for anthropometric traits diverged considerably between AN and BED, suggesting divergent underlying

biology in body mass regulation.

Overall, these studies provide a useful 'first look' at the possible genetic factors involved in BED, however, given the small number of studies, the absence of replication studies, and the frequent reliance on small samples, findings should be viewed as preliminary. Future GWAS with larger sample sizes will be helpful in clarifying allelic variants which pose genetic risk for BED, as well as relevant gene by environment interactions. Indeed, findings from two ongoing GWAS in BED are anticipated (Bulik et al., 2020; Bulik et al., 2021).

1.3 Neurobiology of BED

1.3.1 Neuroendocrinology of BED

Studies of BED endocrinology are limited, and findings are mixed. Nevertheless, the available literature provides evidence that altered neuroendocrine functioning is associated with binge eating. This literature suggests that alterations to central and peripheral hormones involved in food-intake regulation, stress, and reward processing may have a direct pathogenetic role in promoting and/or maintaining binge eating in BED (Marciello et al., 2020).

1.3.1.1 Hypothalamic-Pituitary-Adrenal (HPA) Axis

The HPA axis is one of the main stress response pathways and, given that stress is a well-established precursor to binge eating, several studies have examined HPA axis functioning in BED (Marciello et al., 2020). The HPA axis is a hormonal response to stress which is modulated by excitatory and inhibitory neurotransmitter systems in the hypothalamus. During conditions of stress, hormones are released from the hypothalamus (corticotropin-releasing factor [CRF] and arginine vasopressin [AVP]) into the blood vessels which connect the hypothalamus and the pituitary gland. These hormones stimulate the anterior pituitary gland prompting the secretion of adrenocorticotropic hormone (ACTH) into the blood stream. ACTH then induces glucocorticoid (primarily cortisol) synthesis and release from the adrenal glands, located in the kidneys (Stephens & Wand, 2012).

Studies of HPA axis functioning in BED have yielded inconsistent results. Some have reported significant positive correlations between circulating cortisol levels and self-reported binge eating behaviour (Coutinho et al., 2007; Gluck, 2006; Gluck et

al., 2004a; but not Monteleone, et al., 2000; Monteleone et al., 2003). Similarly, some studies have reported a greater cortisol response to stress in individuals with obesity with BED than individuals with obesity without BED (Gluck et al., 2004a; Gluck, et al., 2004b; but not Schulz, et al., 2011), while others have suggested a downregulation of the HPA axis in patients with obesity who meet criteria for BED (Larsen et al., 2009; Lavagnino et al., 2014; Rosenberg et al., 2013). Studies have also attempted to disentangle the effects of obesity on HPA axis functioning from those of binge eating in BED, however, the nature of the relationship remains elusive. One study has reported a significant positive correlation between the cortisol response during stress and waist circumference in women with obesity and BED but not in those without BED (Gluck et al., 2004a), suggesting that binge eating may mediate the relationship between stress and obesity-related metabolic abnormalities. However, later studies failed to replicate this finding (Chao et al., 2016; Larsen et al., 2009).

Overall, the available evidence suggests that altered HPA axis may be common among people with BED, although the nature of this dysfunction remains unclear. Inconsistent findings may be explained by the wide range of methods used to measure cortisol levels/response, heterogeneity in clinical and control samples used, and/or by psychiatric comorbidities that may differently affect HPA axis functioning. Indeed, dysregulation of the HPA axis has been documented in mood and anxiety disorders (Watson & Mackin, 2006), which frequently co-occur with BED (Udo & Grilo, 2019).

1.3.1.2 Gastrointestinal Tract and Adipose Tissue Hormones

Substances produced in the gastrointestinal tract and adipose tissue also play a crucial role in food-intake regulation, and altered pre- and post-meal peptide signalling may contribute to disturbed food intake (i.e., binge eating) in BED. Orexigenic (appetite-stimulating, e.g., ghrelin) and anorexigenic (appetite-reducing, e.g., cholecystokinin [CCK], glucagon-like peptide-1 [GLP-1], peptide YY, and leptin) peptides act as signals for brain structures involved in homeostatic regulation (e.g., the hypothalamus), reward system functioning (e.g., the striatum) and cognitive control (e.g., the prefrontal cortex) (Marciello et al., 2020). With regards to appetite-stimulating hormones, two studies have reported that individuals with obesity with BED exhibit lower pre- and post-meal total ghrelin levels than controls with obesity

without BED (Geliebter, et al., 2004; Monteleone, et al., 2005a). This suggests that disturbed ghrelin signalling may contribute to binge eating behaviour. However, as study sample sizes were small [n = 24 in Geliebter et al. (2004) and n = 47 in Monteleone et al. (2005a)] and neither study matched cases and controls for BMI, it is possible that this association may be explained by weight, such that higher body weight is associated with lower levels of pre- and post-meal total ghrelin. Indeed, in both studies mean BMI was significantly higher in the group with BED, as opposed to the group with obesity only. Nevertheless, Geliebter, et al. (2008) found that, following brief cognitive behaviour therapy (CBT) and dietetic support, normal concentrations of pre-meal total ghrelin were observed in women with obesity and BED (n = 10), suggesting that pre-meal ghrelin release may normalise with recovery.

Studies have also reported blunted post-meal levels of a range of satiety-inducing peptides, including CCK, GLP-1, peptide YY, and leptin, in BN and BED. For example, two studies have examined post-meal GLP-1 release in participants with BN (Dossat et al., 2014) and participants with obesity with BED (Geliebter et al., 2008). These report that BN and obesity with BED are associated with blunted post meal GLP-1 release relative to healthy-weight, but not obese, controls (Culbert et al., 2016). However, given that participants with BN were, on average, overweight (mean BMI = 28.6), alterations to satiety producing hormones may be more closely related to weight than binge eating behaviour. Higher fasting levels of peptide YY but similar post-meal peptide YY release have also been reported in individuals with obesity with BED compared to individuals with obesity without BED (Marciello et al., 2020). Thus, dysregulation in sensitivity to PYY's satiating signals may also contribute to elevated hunger and overeating in participants who meet criteria for both obesity and BED. Leptin, which is secreted from the adipose tissue, also acts as a satiety signal in the hypothalamus, and altered leptin secretion has been reported in obesity with and without BED (Geliebter et al., 2005; Geliebter et al., 2004).

Finally, reduced insulin sensitivity may also influence binge eating behaviour. For example, in BED, some studies have reported that fasting levels of adiponectin, a protein hormone produced by adipocytes that modulate insulin sensitivity, are decreased in women with BED (with and without obesity), when compared with healthy-weight controls with no history of ED (Abraham, et al., 2014; Monteleone et al., 2003, not Geliebter et al., 2005), although this may be explained by differences in

BMI. Indeed, insulin resistance is a common obesity-related sequelae.

1.3.1.3 Endocannabinoids

The endocannabinoid system, consisting of two cannabinoid receptors (CB1 and CB2) and the endogenous ligands anandamide (arachidonoylethanolamide [AEA] and 2-arachidonoylglycerol [2-AG]), influences homeostatic and hedonic feeding behaviour (Cota et al., 2003), and alterations in endocannabinoid signalling have been reported in BED (Marciello et al., 2020). In a first study, plasma levels of AEA and 2-AG were measured in healthy-weight women with no history of ED (n = 15) and women with AN (n=15), BN (n = 12) and BED with and without obesity (n = 11). Relative to healthy controls, plasma concentrations of AEA were increased in women with BED, but not BN or AN, and there was no significant difference in plasma levels of 2-AG between women with BED and healthy-weight controls (Monteleone et al., 2005b). The authors suggested that this reflects an endocannabinoid-induced potentiation of the drive to eat, possibly contributing to elevated levels of binge eating in BED. Moreover, it was suggested that in women with BED, the enhanced levels of plasma AEA could reinforce the hedonic properties of binge eating, thus perpetuating binge eating behaviour. Consistent with this hypothesis, a subsequent uncontrolled pre/post study showed distinctive responses of endocannabinoids to food-related rewards in participants with obesity and BED before and after food consumption (Monteleone et al., 2017). Specifically, Monteleone and colleagues (2017) found that plasma levels of AEA decreased after eating non-favourite food and increased after eating a favourite food. Moreover, self-reported sensations of “urge to eat” and of “pleasantness while eating" were positively correlated with meal-induced secretion of peripheral AEA, while self-reported sensations of “pleasantness while eating” and the amount of food eaten were positively correlated with meal-induced production of peripheral 2-AG.

1.4 Executive functioning in BED

Executive functioning (also termed ‘cognitive control’) is a multidimensional construct which refers to the collection of “top-down” processes that allow individuals to adapt information processing and behaviours according to their goals (Diamond, 2013). These processes, which rely on prefrontal and subcortical neural systems, are integral components of self-regulation and are essential for adaptive

emotional, social, and physical functioning (Hofmann et al., 2012). Executive dysfunction has been reported in BED; indeed, neuropsychological studies have described difficulties across inhibitory control, attentional control, cognitive flexibility, problem solving and decision-making domains (Blume et al., 2019; Boswell & Grilo, 2021; Cury et al., 2020; Iceta et al., 2021; Smith et al., 2018). However, findings are inconsistent and inconclusive (Cury et al., 2020), so the exact nature of the BED neuropsychological phenotype remains unclear.

1.4.1 Response inhibition

One prominent line of inquiry relates to difficulties with inhibition control and, by extension, impulsivity (Gullo et al., 2014). Here, inhibition control refers to the overriding of a planned or already initiated action (e.g., responding to a stimulus, or seeking a reward; Bari & Robbins, 2013), and it is hypothesised that BED may be characterised by difficulties inhibiting pre-potent actions, particularly in the context of high-calorie food (e.g., Balodis et al., 2013). However, at present it is not clear if inhibitory control processes are impaired in obesity in general or more specifically related to binge eating behaviour, and therefore BED. Indeed, reduced inhibition control has been reported in individuals with obesity with and without BED, when compared to controls with "healthy" weight, but at times these groups do not differ from each other (Lavagnino et al., 2016), suggesting that cognitive impairment may not solely be related to binge eating.

Two recent meta-analyses of studies using the Stop Signal Task concluded that there was no significant difference between participants with obesity and BED, versus participants with obesity without BED (Lavigno et al., 2016; Cury et al., 2020). Similarly, where inhibitory control has been assessed using the go/no-go paradigm findings are inconsistent. While two studies have reported that participants with BED make more commission errors (i.e., 'false alarm' responses) than controls with obesity (Cordova et al., 2017; Hege et al., 2015), several other studies observed no evidence for a difference between BED and obesity (Blume et al., 2018; Kollei et al., 2018; Loeber et al., 2018; Lyu et al., 2017; Oliva et al., 2019) or normal weight comparison groups (Kollei et al., 2018; Loeber et al., 2018). Of note however, studies reporting no difference between BED and obesity frequently identified other factors which may moderate differences between-groups (Lyu et al., 2017; Kollei et al., 2018; Loeber et al., 2018; Oliva et al., 2019). For example, Kollei et al (2018)

observed that self-reported hunger significantly influenced task performance by increasing inhibition deficits to high-caloric stimuli in participants with BED, but not those without BED. Similarly, Loeber et al (2018) reported that differences between participants with BED, obesity and normal weight were moderated by restrained eating behaviour and mood. Specifically, the authors reported that participants with obesity and BED made more commission errors on trials involving food-related stimuli when they also reported restrained eating behaviours and current positive mood. Heterogenous findings may also be explained by differences between the tasks used to assess response inhibition. Indeed, neuroimaging studies in healthy samples have shown that withholding a response (as in the go/no-go task) and stopping a response (as in the stop signal task) involve overlapping yet distinct neural and molecular mechanisms (Eagle et al., 2008; Swick et al., 2011).

Only a handful of neuroimaging studies have been published to date and only two of these have investigated response inhibition. In one study using a food-specific go/no-go task during magnetoencephalography (MEG), individuals with obesity with BED (n=13) showed lower recruitment of prefrontal brain regions during response inhibition (i.e., no-go trials) than controls with overweight or obesity (n = 14), despite comparable task performance (i.e., equivalent reaction times and accuracy; Hege et al., 2015). Specifically, it was reported that withholding a response (i.e., successful no-go) was associated with stronger activity in the right dorsolateral prefrontal cortex (DLPFC) and the left and right superior medial prefrontal areas, and that, compared to participants with obesity, participants in the BED group showed weaker activity in these regions for trials using food (as opposed to toy) stimuli that required a no-go response. In another study, the colour-word Stroop task was administered to adults with obesity and BED (n = 11), adults with obesity without BED (n = 13), and adults with "healthy" weight (n = 11) during functional magnetic resonance imaging (fMRI). Here, it was reported that mean blood oxygen-level dependent (BOLD) signal for the Stroop effect (i.e., contrasting incongruent trials with congruent trials) was diminished in the ventromedial prefrontal cortex (vmPFC), inferior frontal gyrus (IFG), and insula in the BED group, relative to controls with and without obesity (Balodis et al., 2013), and that reduced BOLD signalling in the right IFG and vmPFC was negatively correlated with dietary restraint in BED participants. Together, these findings suggest that BED may be

distinguished from obesity by a diminished ability to recruit impulse-control-related brain regions, and that this may contribute to difficulties with food-intake regulation in BED. However, more studies in larger samples are needed.

1.4.2 Attention control

Attention control refers to the ability to select and direct attention to stimuli that are goal relevant. This process has been divided into three sub-processes — alerting, orienting, and cognitive interference control, also called executive control of attention (Petersen & Posner, 2012). Alerting refers to the ability to focus attention on upcoming events and involves responding to a cue with an alert state that is then maintained. Orienting and reorienting relate to shifting attention to a stimulus outside one's current focus. Cognitive interference control involves ignoring or suppressing irrelevant information or a competing stimulus in order to maintain a goal. It is proposed that difficulties with cognitive interference control may contribute to difficulty inhibiting attention to urges or cravings and, therefore, drive binge eating behaviour (Voon, 2015). In line with this, meta-analysis of behavioural studies which investigated cognitive interference control in binge-type eating disorders concluded that overall, binge-type EDs showed difficulties with interference control, relative to healthy controls, and that difficulties were most pronounced in the context of high-calorie food (Wu et al., 2013).

Relatedly, studies have shown the presence of food-related attention biases in individuals with eating and weight disorders. These studies suggest that individuals with obesity and BED tend to be hyper-vigilant to food stimuli, particularly high-calorie food stimuli, and experience difficulty turning attention away from food (Brooks et al., 2011; Hendrikse et al., 2015). This attention bias towards food is common in the population with obesity (Castellanos et al., 2009; Nijs & Franken, 2012; Nijs et al., 2010; Werthmann et al., 2011) and, therefore, may be related to increased BMI. Indeed, it has been shown that increased BMI is associated with increased attention bias towards food words in a Stroop task (Calitri et al., 2010), and that weight loss following bariatric surgery was associated with reduced attention bias towards food at 6-month follow-up (Giel et al., 2014). However, attention bias towards food may be more severe among individuals who binge eat (Albery et al., 2016; Schag et al., 2013; Stojek et al., 2018), suggesting that factors beyond high BMI may contribute to food-related attention disturbance.

Attention bias models of binge eating behaviour emphasise the role of appetitive motivation and incentive salience (Berridge, 2009). Thus, the presence of an attention bias towards food is indicative of elevated food-related reward sensitivity. These models suggest that conditioned palatable food cues (i.e., high-calorie food cues) elicit attention bias toward those stimuli, exacerbating cravings and motivation to eat, resulting in binge eating episodes (Stojek et al., 2018). Consistent with this hypothesis, several studies using eye-tracking to evaluate visual attention for food have shown that, when compared to age and weight-matched controls without BED, adults with BED show delayed disengagement from high-calorie food and body stimuli at long stimulus durations (Popien et al., 2015; Schag et al., 2021; Svaldi et al., 2011) and rapid orienting to food stimuli, in general, at short (i.e., pre-attentive) presentation durations (Schmitz et al., 2014; Svaldi et al., 2015). Moreover, an eye-tracking study in adolescents found that participants with BED were quicker to identify food, as opposed to non-food stimuli in a visual search task, and that adolescents with BED had greater difficulty disengaging with high- and low-calorie food cues than controls matched for age and BMI (Schmidt, et al., 2016). Similarly, studies using visual probe paradigms have reported hyper-vigilance for high-calorie food stimuli in BED, as demonstrated by short response latencies when the probe replaced a food, as opposed to non-food, stimulus (Deluchi et al., 2017; Schmitz et al., 2014), and difficulties disengaging with food stimuli, as demonstrated by longer response latencies when food-stimuli were presented for longer periods of time (Deluchi et al., 2017 but not Schmitz et al., 2014).

Neurophysiological and neuroimaging studies also lend support to the attention-bias model for BED, with converging evidence pointing to altered function in cortical and striatal regions. The striatum and insula have been associated with reward sensitivity and impulsivity in BED. For example, in a study that investigated high-calorie food cue reactivity in adults with BN (n = 14) and BED (n = 17), compared to controls with normal weight (n = 18) or obesity (n = 17) it was reported that BOLD signal in the left ventral striatum following food cue (as oppose to neutral cue) exposure was stronger in participants with BED than in those with BN, and that BOLD signal in the right ventral striatum following food cue (as opposed to neutral cue) exposure was stronger in participants with BED than in those with obesity or normal weight (Weygandt et al., 2012). In another study, reward anticipation during go/no go trials

using food (as opposed to neutral) stimuli, was associated with bilateral decreases in ventral-striatal activation in individuals with obesity and BED, relative to participants with obesity only (Balodis et al., 2013). Additionally, imaging studies have described functional differences between participants with and without BED in prefrontal networks (diminished BOLD signalling in BED) associated with habitual learning (Voon, 2015) and impulse control (Balodis et al., 2015; Hege et al., 2015), as well as structural differences (reduced grey-matter volume) in the anterior-cingulate and medial-orbitofrontal cortices (Balodis et al., 2015).

1.5 Emotion dysregulation

It has been proposed that the relationship between negative affect and BED may depend on a person's ability to regulate their emotions. Indeed, a substantial body of literature suggests that binge eating functions to mitigate negative affect (e.g., Berg et al., 2015; Leehr et al., 2015) and that, therefore, emotion dysregulation may increase risk of binge eating. Accordingly, emotion regulation models for binge eating have proposed that high levels of negative emotionality may predispose individuals to engage in binge eating as a means of suppressing, alleviating, or avoiding negative emotions (Heatherton & Baumeister, 1991; Polivy & Herman, 1993). In this way, binge eating behaviour may be maintained by reduced ability to recognise emotions and resist emotion-driven impulses, and/or a reliance on maladaptive emotion regulation strategies (Harrison, Sullivan, Tchanturia, & Treasure, 2010). Indeed, studies have shown that individuals with BED show greater difficulty applying adaptive emotion regulation strategies, such as cognitive reappraisal, than healthy controls (e.g., Dingemans & van Furth, 2012) and that greater reliance on maladaptive emotion regulation strategies is correlated with greater ED symptom severity (Gianini, et al., 2013; Harrison, et al., 2016; Lavender et al., 2015; Lavender et al., 2014; Pisetsky, et al., 2017).

Overall, there is strong empirical support for the emotion-regulation hypothesis (Cardi et al., 2015; Dingemans et al., 2017; Haedt-Matt & Keel, 2011; Leehr et al., 2015). First, findings from experimental studies generally confirm that negative emotion serves as an antecedent to binge eating (Agras & Telch, 1998; Chua, et al., 2004; Gluck, et al., 2004; Hilbert, et al., 2010; Laessle & Schulz, 2009; Rosenberg et al., 2013; Schulz & Laessle, 2012; but not Dingemans, et al., 2009; Munsch, et al., 2008; Telch & Agras, 1996). Similarly, studies using ecological momentary

assessment to longitudinally assess the effect of emotion on eating behaviour in the natural environment ubiquitously indicate that binge eating is preceded by strong emotional experiences, albeit not always negative (Berg et al., 2017; Bodell et al., 2019; Goldschmidt et al., 2012; Hilbert et al., 2009; Hilbert & Tuschen-Caffier, 2007; Munsch et al., 2012; Schaefer et al., 2020; Stein et al., 2007). Second, regarding the relief component of the emotion regulation model - that is, the proposal that mood improves after binge eating – findings are mixed and limited. While some studies have reported post-binge eating reductions in negative affect (Berg et al., 2017; De Young et al., 2013; Smyth et al., 2007), others have reported that negative emotion was unchanged following an episode of binge eating (e.g., Hilbert et al., 2007; Schulz & Laessle, 2010). However, methodological differences relating to timing and method of pre- and post-binge mood assessment may go some way towards explaining the heterogenous findings reported.

Emotion regulation ability has been conceptualised as a cognitive control function involving attention control and higher-order cognitive abilities such as working memory, long term memory, learning, judgement and reasoning (Ochsner & Gross, 2005). Studies conceptualising emotion regulation in this way highlight that emotion regulation is an inherently goal-directed behaviour (e.g., Aldao & Tull, 2015; Bonanno & Burton, 2013; Gross, 2015). In particular, they emphasise that control of attention towards or away from emotions and the practice of cognitively changing the meaning of, or salience of, emotionally evocative stimuli, are key components of emotion regulation (Ochsner & Gross, 2005; Gross, 2015). This framework is supported by evidence from neuroimaging studies which consistently show that the use of adaptive emotion regulation strategies, most notably cognitive reappraisal, engages the frontoparietal network, including the dorsolateral, dorsomedial, and ventrolateral regions of the prefrontal cortex (i.e., regions central to cognitive control) (Pruessner et al., 2020). As such, it is possible that the emotion dysregulation which is characteristic of BED may reflect more generalised difficulties with cognitive control.

1.6 Treatment for BED

Evidence-based treatments for BED which are recommended by international guidelines include psychological therapies and pharmacotherapy (Giel, Bulik, et al., 2022). These treatments aim to facilitate a reduction in or abstinence from objective binge eating behaviour and reduce associated ED psychopathology (e.g., craving for food, concerns about body image, etc). They also aim to achieve improvement in mood and other psychiatric symptoms, improvement in metabolic indicators of physical wellbeing, and improvement in quality of life (Giel, Bulik, et al., 2022). Importantly, weight-related treatment targets in BED are controversial, and best-practice guidelines instead prioritise behavioural outcomes as a primary treatment goal for BED. Nevertheless, lifestyle interventions, which typically include weight-related treatment targets (e.g., behavioural weight loss), have been studied and are frequently applied in this population (Hilbert et al., 2020).

Psychotherapy and self-help interventions are recommended as a first-line intervention for BED. Psychotherapy, most commonly based on cognitive behaviour therapy (CBT), has been shown to produce significant long-term improvements in binge eating and associated psychopathology, as well as significant reductions in BMI which endure for 12 months following treatment (Hilbert et al., 2020). RCTs of CBT in BED are more numerous than studies using other conceptually and procedurally distinct psychotherapies (e.g., interpersonal psychotherapy or psychodynamic therapy). However, no evidence for CBT superiority has been reported (i.e., other psychotherapies with specific interventions for BED may be equally efficacious) (Hilbert et al., 2020). Similarly, outcomes from structured self-help treatment have been shown to be comparable to those achieved through psychotherapy (Hilbert et al., 2019). It is estimated that 53% (95% CI: 45-61) of patients seeking psychotherapy for BED respond well to treatment (Hilbert et al., 2020): that is, they achieve a clinically meaningful reduction in or remission from binge eating behaviour by the end of treatment. In general, those who respond well to treatment tend to start therapy with low level binging and report an early decrease in binge frequency. Alternatively, rapid response to treatment, typically defined as a 65% to 70% reduction in binge eating in first four weeks of treatment, has also been shown to be a significant positive prognostic indicator of recovery (Vall & Wade, 2016; Hilbert et al., 2020).

Behavioural weight loss (BWL) is not a treatment for BED, but, given that BED and obesity commonly co-occur, BWL is frequently prescribed (Hilbert et al., 2020). These interventions aim to encourage weight loss through increased energy expenditure and reduced energy intake, and they emphasise self-monitoring practices (e.g., tracking of food consumption and exercise) and the implementation of small, incremental lifestyle changes, as well as weight-loss targets. In RCTs, psychotherapy generally outperformed BWL treatment in reducing binge eating episodes and ED psychopathology in the short term (post-treatment) and led to a significantly higher remission from binge eating in the longer term (follow-up) (Hilbert, 2019; Hilbert et al., 2020). In addition, although some studies have concluded that BWL was associated with greater weight loss in the short term, no differences were maintained at follow-up (Hilbert, 2019). Thus, BWL treatment was found to be less suited for the treatment of binge eating symptomatology than psychotherapy.

With respect to pharmacotherapy, studies have examined whether second-generation antidepressants, anticonvulsants, and central nervous system stimulants, may alleviate symptoms and facilitate weight loss in BED (Hilbert, 2019). Each of these agents has been found to provide greater relief from symptoms than placebo, however, few facilitate weight loss. Due to its effectiveness across both aforementioned domains, in 2015, lisdexamphetamine (LDX), a central nervous system stimulant, became the first drug to be approved by the Food and Drug Administration for the treatment of BED (Schneider et al., 2021). However, the effect of LDX on ED psychopathology and mood remains unclear, and data on long-term maintenance of effects are lacking. There are also significant risks associated with the drug's use; little is known about the effects of long-term administration, and rates of adverse events and premature discontinuation of the drug were elevated in RCTs (Hilbert et al., 2020; Schneider et al., 2021).

There is some evidence to suggest that antidepressant treatment may support remission from BED. A meta-analysis of seven RCTs (six with SSRIs and one with a tricyclic) showed significantly higher remission rates in the antidepressant, as opposed to the placebo, group (40.5% versus 22.2%; Stefano, et al., 2008). Similarly, preliminary data suggest that the selective serotonin and norepinephrine reuptake inhibitor, duloxetine, may be effective for reducing binge eating and depressive symptoms in individuals with BED and co-occurring major depression (Guerdjikova

et al., 2012). Several antiepileptic drugs have also been evaluated in RCTs (e.g., topiramate, zonisamide, and lamotrigine). These trials indicate that antiepileptic drugs may drive significant reductions in binge eating behaviour and promote weight loss, however, drop-out/discontinuation rates were high (up to 47%), suggesting these drugs may not be well tolerated by this population (Carter et al., 2003; McElroy et al., 2009). Weight loss drugs have also been considered for the treatment of BED and, although RCTs generally report weight loss following treatment, effects on binge eating behaviour have been mixed. Moreover, several drugs in this category that may have shown promise have been removed from the market due to safety concerns (e.g., dexfenfluramine, sibutramine and rimonabant) (McElroy et al., 2020). Incretins (e.g., glucagon-like peptide-1 receptor agonists) have yet to be evaluated in BED.

Finally, while it may be intuitive to think that the combination of psychological therapy and pharmacotherapy may have a more potent effect on BED symptoms, there is little empirical support for this hypothesis. Findings from a recent systematic review indicate that this approach significantly enhanced reductions in binge eating and weight in only two of 12 trials (both with antiepileptic medications) and modestly enhanced weight loss, but not binge eating, outcomes in two out of 12 trials (both with the weight-loss medication orlistat) (Reas & Grilo, 2021).

1.7 Novel options for treatment

According to a recent meta-analysis, almost half of BED patients who complete treatment continue to struggle with episodes of objective binge eating after treatment ends (Hilbert et al., 2020), so there remains a pressing need to develop new treatments that make use of the new knowledge we have about BED neurobiology and the new technologies available for intervention. Promising avenues for treatment include neurocognitive training and neuromodulation.

1.7.1 Neurocognitive training

Neurocognitive training aims to achieve behaviour change by enhancing cognitive control (Boutelle et al., 2020). In BED and obesity, these programmes, which are delivered via computer or smartphone, typically target food-related inhibition control or attention bias towards food (Allom et al., 2016; Jones et al., 2016; Turton et al., 2016). Inhibitory control training uses a stop signal or go/no-go paradigm in which

participants are repeatedly asked to inhibit responses to stimuli when presented with a “stop” or “no-go” cue. One feasibility randomised sham-controlled trial (n = 22) examined the effect of three-sessions of food-specific inhibitory control training in adults with BED. During training, pictures of high-calorie food items were presented on the periphery of a computer screen. Those receiving real inhibitory control training, as opposed to sham, were required to suppress the urge to gaze towards these pictures, whereas participants in the sham condition were directed to freely view the screen. Although both the intervention and the control groups decreased binge eating, neither group reported changes in craving for food, food addiction, or liking/wanting for food (Giel et al., 2017). In contrast, a proof-of-concept study (n = 49) which evaluated the effect of a single session food-specific, as opposed to neutral, go/no-go training in women with BN or BED reported no significant differences in eating behaviour or ED symptoms 24 hours after training (Turton et al., 2018). However, the authors suggested that given the significant and chronic nature of ED symptoms in the sample, greater duration and frequency of training sessions may have been needed to see an impact on behaviour.

Another emerging approach to neurocognitive training which has been evaluated for use in eating and weight disorders is attention bias modification training (ABMT). ABMT, which makes use of the visual dot-probe task, aims to reduce attention bias towards food by training people to respond to (and thus attend to) non-food stimuli being presented instead of food stimuli. Alternatively, participants are directed to attend to low-calorie food stimuli and avoid high-calorie food stimuli. Several meta-analyses support the preliminary potential of ABMT for changing appetitive behaviours, although effect sizes are small-medium and few studies measured the long-term maintenance of effects (Fodor et al., 2017; Turton et al., 2016). In obesity, ABMT has been shown to change attention bias towards chocolate and has been associated with reduced chocolate intake (Dickson et al., 2016; Kemps et al., 2014; Schumacher et al., 2016). In fact, one study involving women with obesity (n = 96) showed that a single session of ABMT modified attention bias towards chocolate in the short term (24 hours) and that the effect was maintained to one-week post-treatment (Kemps et al., 2014). In BED, one study (n = 47) reported that a single session of ABMT which aimed to reduce bias towards food was associated with a significant short-term reduction in subjective food craving (Schmitz & Svaldi, 2017),

and an open-label feasibility trial (n = 9) using eight weekly sessions of ABMT reported reduced weight, ED symptoms, binge eating and attention bias towards food after training and at 3-month follow-up (Boutelle et al., 2016).

Relatedly, one randomised control trial has looked at the therapeutic potential for approach bias modification in BN and BED (n = 56) (Brockmeyer et al., 2019). Approach bias modification training involves pushing a joystick away (avoid) or pulling a joystick towards (approach) in response to a food image. Results showed significant reductions in episodes of binge eating, ED symptoms, trait food craving, and food cue reactivity at follow-up. However, food intake, approach bias, and attention bias toward food did not change (Brockmeyer et al. 2019). Taken together, these studies demonstrate that there is good preliminary evidence to suggest that neurocognitive trainings that target food-related cognitive processes may have therapeutic effects in BED. However, trials to date suggest the magnitude of the effect may be modest when neurocognitive training is used as a stand-alone treatment.

1.7.2 Non-invasive brain stimulation (NIBS)

Non-invasive brain stimulation (NIBS) is also emerging as a potentially useful tool for treating psychological disorders, including BED (Dalton et al., 2018; Dalton et al., 2017). Transcranial direct current stimulation (tDCS) is a NIBS technique that may be particularly well suited to the treatment of BED. tDCS is a safe and well tolerated technique which is inexpensive, portable, easy to use, and suitable for remote self-administration (Brunoni et al., 2019; Knotkova et al., 2019). In tDCS, a constant weak direct current is applied via electrodes placed on the scalp to increase (anodal tDCS) and/or decrease (cathodal tDCS) cortical excitability. This stimulation produces widespread diffused activation in the brain. Specifically, tDCS modulates network dynamics within functionally connected areas beyond the cortical regions located beneath the electrodes. As a result, tDCS may modulate task or symptom specific neural networks. These changes in cortical excitability outlast the stimulation period (up to 60 minutes after a single session) and, with repeated administration, may lead to lasting changes in brain function (Brunoni et al., 2019).

Therapeutically, tDCS has been most rigorously investigated in major depression. Here, anodal tDCS applied to the left DLPFC has a reliable antidepressant effect in

non-treatment resistant individuals (Moffa et al., 2018). In EDs, evidence from proof-of-concept studies suggest that tDCS may be effective for the treatment of binge-type EDs. In BN, a proof-of-concept RCT (n = 20) with 24-hour follow-up indicated that a single session of tDCS improves ED psychopathology, reduces craving for food, reduces urge to binge, and improves self-regulatory control during reward related decision making (Kekic et al., 2017). In BED, a single-session RCT (n = 30) using right DLPFC anodal tDCS reported a short-term reduction in craving for food and desire to binge eat in participants who received real tDCS, as opposed to sham (Burgess et al., 2016). This finding was replicated in a recent sham-controlled crossover trial (n = 16): Following a single session of right DLPFC anodal tDCS, improvements in food-related response inhibition and craving for food were observed in participants who received real 2mA tDCS stimulation, as opposed to real-1mA or sham stimulation (Max et al., 2021).

Two studies have examined the effect of multiples sessions of tDCS on BED symptoms. Firstly, a recent randomised sham-controlled trial involving 32 adults examined the effect of 10 sessions of tDCS on attention bias towards food, craving for food, and cognitive flexibility (Afzali et al., 2021). In this trial, tDCS was given with the anode over the left DLPFC and the cathode over the right DLPFC at an intensity of 2mA for 20 minutes. Sessions were three times weekly until 10 sessions had been completed. At post-treatment and 45-day follow-up, real tDCS treatment, as opposed to sham, was associated with a greater reduction in attention bias towards food, greater reduction in craving for food, and greater improvement in cognitive flexibility. However, the effect sizes were small, and the authors acknowledged a number of important limitations to the study. These include a small sample (N=32) with unusually low mean BMI (mean BMI=30.35 kg/m^2), and concerns about the effect of poor eye-tracker calibration on the reliability of attention bias outcomes. Nevertheless, these findings hint that this line of inquiry is worth pursuing.

Secondly, our research group has recently completed an RCT involving 68 participants with BED, where six sessions of tDCS were delivered over 3 weeks, with tDCS given with the anode over the right-DLPFC and the cathode over the left DLPFC (see Gordon, Brockmeyer, Schmidt & Campbell, 2019 for study protocol). In this trial, six sessions of concurrent tDCS and approach bias modification training were administered to adults with BED over 3 weeks. While no significant differences

between real and sham groups were observed, real, as opposed to sham, tDCS with approach bias modification training was associated with a trend for reduced ED symptomology, reduced BMI, and reduced approach bias towards high-calorie foods at post-treatment and 8-week follow-up (Gordon, *unpublished thesis*). Moreover, qualitative findings revealed that participants viewed the treatment as tolerable and acceptable (Gordon, Williamson, et al., 2021).

This "online" approach, where tDCS is combined with another neurocognitive training, is a promising avenue for optimising tDCS treatment. Given that the efficacy of tDCS depends on the functional state of the brain at the time of stimulation, greater and longer-lasting neuroplastic effects could be achieved when tDCS and neurocognitive training co-activate a disorder-related neural network (Vanderhasselt & Ottaviani, 2022). This may be because, by altering the relationship between excitatory (glutamatergic) and inhibitory (GABAergic) systems in the brain (Krause et al., 2013), tDCS creates optimal conditions for memory reconsolidation, a process which may re-enforce the new learning which takes place during neurocognitive training. Similarly, when disorder-related stimuli are used, neurocognitive training promotes the activation of disorder relevant brain regions, thereby enhancing the effectiveness of stimulation. Consistent with this hypothesis, several RCTs have reported that concurrent tDCS and neurocognitive training produced superior outcomes from treatment in adults with anxiety disorders (Heeren et al., 2015; Heeren et al., 2017) depression (Moffa et al., 2018) and substance use disorders (Rigi Kooteh, et al., 2019; but not den Uyl, et al., 2018; den Uyl, et al., 2017).

Given promising preliminary findings from studies using tDCS as a stand-alone treatment or adjunct to neurocognitive training in BED, continued exploration of concurrent tDCS with neurocognitive training is warranted. While there are a number of good candidate adjuncts to tDCS treatment in BED, ABMT may be particularly well suited to delivery alongside tDCS: it is computer-based and can be carried out independently and it has demonstrated efficacy when delivered as a stand-alone treatment in BED. Moreover, previous studies have shown that tDCS augments attention bias towards salient stimuli (Khajehpour et al, 2022; Clarke et al, 2020; Heeren et all, 2015), including food (Afzali et al., 2021), and trials in other psychiatric disorders have shown that, when tDCS and ABMT are delivered

simultaneously, tDCS may enhance outcomes from ABMT (Myruski et al., 2021). Given the recent arrival of tDCS devices intended for supervised self-administration, both ABMT and tDCS can now safely be provided at home, thereby increasing their accessibility and scalability. This is particularly important given the recent surge in demand for remotely delivered interventions. Accordingly, this thesis will explore the therapeutic potential for combining at-home tDCS with food-specific ABMT in adults with BED.

1.8 Thesis Overview

Studies suggest that AB towards emotion may contribute to the maintenance of psychological disorder. NIBS, which has been shown to alter emotional experience (i.e., mood), may achieve therapeutic effects by altering emotional AB. In *Chapter 2*, we present a meta-analysis of studies assessing the effect of NIBS targeting the DLPFC on emotional AB. Meta-analytic findings showed that there is presently limited evidence to suggest that NIBS of the DLPFC alters emotional AB. However, null findings may be explained by methodological heterogeneity or ceiling effects where healthy samples were used (~2/3 of studies). Indeed, more than 80% of studies in clinical samples concluded that NIBS altered AB. As such, we recommend continued research in clinical samples which addresses the limitations discussed.

Importantly, AB may occur in the context of other salient stimuli. Indeed, AB towards food has been described in obesity with and without BED. Understanding the extent to which AB towards food distinguishes BED from simple obesity may be useful for the development of novel interventions. In *Chapter 3,* we examine AB towards food in adults with obesity with and without BED using a visual probe task with eye-tracking. We observed that both groups showed an AB towards high-calorie food however, only participants with BED showed AB towards low-calorie food. Additionally, we observed that craving for food, which was significantly higher in participants with BED, was significantly correlated with AB towards high-calorie food. As a result, our findings indicate that interventions that directly target AB towards high-calorie food may have therapeutic potential in BED.

Accordingly, *Chapter 4* of this thesis presents a protocol for a randomised controlled feasibility study of concurrent at-home tDCS with ABMT in adults with BED. Findings from this trial are presented in *Chapters 5 and 6* of this thesis. Overall, results indicated that the intervention was feasible and acceptable, and associated with reductions in objective binge eating behaviour, symptoms of low mood, BMI and AB towards high-calorie food stimuli which were maintained to follow-up.

Finally, *Chapter 7* provides a general discussion of the findings presented in thesis. Here, key findings are summarised and synthesised with the wider literature relating to neurocognitive training, neuromodulation, and BED. Strengths and limitations are explored and recommendations for future research are presented.

Chapter 2. The effect of non-invasive brain stimulation targeting the dorsolateral prefrontal cortex (DLPFC) on attention bias towards emotion: A systematic review and meta-analysis

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Author contributions: The review was conceived by the candidate, Professor Ulrike Schmidt, and Professor Iain Campbell. The literature search was conducted by the candidate and Amelia Hemmings. Data extraction was conducted by the candidate and Dr Bethan Dalton and checked by Amelia Hemmings and Dr Lauren Robinson. The quality assessment for included papers was completed by the candidate, Basak Ince, Lucy Hyam, Mariana de Padua-Lopes. The candidate completed the data synthesis and meta-analysis with statistical supervision by Dr Lauren Robinson. The candidate authored the chapter with constructive feedback from her supervisors.

Abstract

Background: Attention bias (AB) towards negative emotions has been implicated in the development and maintenance of psychiatric disorders, such as depression and anxiety. This AB towards emotion may reflect altered cognitive control of attention, whereby strong "bottom-up" responses to salient emotional stimuli compromises the "top-down" control of attention. The dorsolateral prefrontal cortex (DLPFC) is a key component of the cognitive control network and a common target for non-invasive brain stimulation (NIBS). As such, the therapeutic effects associated with NIBS targeting the DLPFC may be related to changes in AB. Thus, we conducted a systematic review and meta-analysis to investigate the effect of a single session of NIBS targeting the DLPFC on AB towards emotion in healthy and clinical samples.

Method: A systematic review of the literature was conducted using PsychINFO, Medline, and Embase databases to identify articles examining the effects of a single session of transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS) and theta burst stimulation (TBS) targeting the left or right DLPFC on AB towards emotion in samples with or without psychiatric disorder. Both up-regulating and down-regulating variants were considered. 35 studies met inclusion criteria. Participants (n = 1, 532) were mostly female (67.3%) and had a mean age 26.4 years. Results from individual studies were converted to Hedge's g and random-effects models were used to estimate the overall effect size.

Results: We found no significant overall effect of unilateral excitatory stimulation targeting the left (g = -*.124,* p = .265) or right (g = .246, p = .149) DLPFC on AB towards emotion. We also found no significant effect for bilateral stimulation of the DLPFC on AB towards emotion (g = -0.318, p = .139). Few studies applied inhibitory stimulation to the left or right DLPFC and, overall, findings from these studies were mixed.

Conclusion: Overall, there is limited evidence to suggest that NIBS targeting the dorsolateral prefrontal cortex (DLPFC) alters emotional AB. However, as the literature was highly heterogenous, these findings should be viewed with caution. Future studies in samples with baseline AB towards emotion (e.g., clinical samples) using brief multi-session protocols (e.g., 3 sessions) and methodologically sound outcome measures are needed to clarify the effect of NIBS on AB towards emotion.

2.1 Introduction

The way in which we respond to emotional challenges is a key determinant of psychological wellbeing. Accordingly, emotion regulation and the ways in which it may be improved are key areas for research in psychological medicine. Emotion regulation refers to the initiation of new, or the alteration of ongoing, emotional responses through a range of regulatory processes (Ochsner & Gross, 2005). These processes exist along a continuum ranging from explicit to implicit (i.e., initiated with or without conscious awareness), and controlled to automatic (i.e., governed by voluntary "top-down" or stimulus driven "bottom-up" processes) (Braunstein et al., 2017).

Explicit-controlled forms of emotion regulation, most notably cognitive reappraisal, are thought to be the most effective strategies for regulating negative emotion (Gross, 2014). The voluntary allocation of attention towards or away from emotional stimuli (i.e., selective attention) is an explicit-controlled form of emotion regulation which has been linked to reappraisal ability (Braunstein et al., 2017). Indeed, cross-sectional studies have shown that reappraisal of negative emotional scenes is more effective when one pays less attention to negative components of the scene (Manera et al., 2014; van Reekum et al., 2007). Similarly, successful down regulation of negative affect via reappraisal has been associated with initial attention towards negative stimuli, allowing for their initial processing, followed by subsequent shifts away from them (Strauss et al., 2016). However, attention is captured by stimuli with high emotional or motivational valence in a more automatic (i.e., "bottom-up") fashion (Lang & Bradley, 2010; Pourtois et al., 2013; Vuilleumier, 2005). Typically, this preference for emotional information can be modulated via cognitive control processes to facilitate goal-directed behaviour. However, when cognitive control resources are depleted or bottom up responses are exaggerated, attention bias (AB) may emerge (Braunstein et al., 2017; Todd et al., 2012).

AB occurs during the early stages of information processing and refers to a tendency to preferably detect, orient to, and attend to emotionally salient stimuli, as opposed to neutral ones (MacLeod & Mathews, 2012; Mathews & MacLeod, 2005). The hypothesis that AB influences emotion regulation is supported by findings from a number of experimental studies. For example, studies that used eye-tracking to assess gaze patterns when completing directed emotion regulation tasks have shown that AB toward negative stimuli is cross-sectionally correlated with poorer implementation of

emotion regulation strategies. This was particularly true of cognitive reappraisal which demands higher levels of "top-down" control than other strategies investigated (e.g., suppression or distraction) (Bebko et al., 2011; Manera et al., 2014; Strauss et al., 2016; van Reekum et al., 2007). Relatedly, AB for negative and/or threatening emotional stimuli is a well-established transdiagnostic feature of psychological disorder. For example, studies have shown that when shown an array of emotional stimuli (e.g., faces), depressed individuals and those with elevated symptoms of low mood selectively attend to the negative rather than neutral or positive stimuli (Armstrong & Olatunji, 2012; De Raedt & Koster, 2010; Le Moult & Gotlib, 2019; Peckham et al., 2010). Similarly, studies have shown that individuals with anxiety disorders or elevated trait anxiety show an AB towards threat which is reliably demonstrated with different paradigms and under a variety of experimental conditions (Bar-Haim et al., 2007).

Neuroimaging studies of emotion regulation have provided some insight into the mechanisms that may be involved. Findings from several studies in healthy adults suggest that a functionally connected network of cortico-limbic pathways may play a central role in the top-down cognitive control of emotional experience (Johnstone et al., 2007; Ochsner & Gross, 2005, 2008; Seminowicz et al., 2004; Wager et al., 2008), although the exact nature of this system remains unclear. Broadly, leading theories argue that during explicit-controlled emotion regulation, prefrontal activity, particularly that relating to the dorsolateral prefrontal cortex (DLPFC), reduces negative emotion by influencing subcortical systems implicated in affective appraisal and learning processes which, in turn, impact emotional experience (e.g., Wager et al., 2008). Indeed, a number of functional neuroimaging studies have observed that the DLPFC initiates emotion regulation by causing inhibition of the amygdala (e.g., Siegle, et al., 2007). Conversely, AB appears to be associated with increased activation in the amygdala (Wager et al., 2008), which may indicate reduced ability to mobilise the DLPFC resources needed to initiate "top-down" emotion regulation. In addition, hemispheric specialisation of emotional processing has also been proposed, with some studies suggesting that activation in the left DLPFC may be associated with positive mood and the processing of positive stimuli, whereas activation in the right DLPFC has been linked to negative mood and the processing of negative stimuli (Canli et al., 1998; Herrington et al., 2010; Liu et al., 2016; Spielberg et al., 2008).

Recently, a number of studies have investigated whether non-invasive brain stimulation

(NIBS) targeting prefrontal regions, most commonly the DLPFC, may influence emotional AB. NIBS techniques alter cortical excitability in superficial regions of the cortex with relatively high levels of precision and may produce neuroplastic effects that outlast the stimulation period (~up to 60 minutes following a single session) (Brunoni et al., 2019). Variants of NIBS include transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), and theta burst stimulation (TBS). In tDCS, a constant weak direct current is applied via electrodes placed on the scalp to increase (anodal tDCS) and/or decrease (cathodal tDCS) cortical excitability (Brunoni et al., 2019). In rTMS, an electromagnetic field is created by an electric current passing through a coil which is placed on the scalp directly above the target region. This produces a secondary electromagnetic field which alters cortical excitability as a function of stimulation frequency, with high frequency (typically 10 Hz) and low frequency (typically 1 Hz) stimulation increasing and decreasing cortical excitability, respectively (Brunoni et al., 2019). In TBS, a variant of rTMS, stimulation is applied in bursts of three at high frequency (50 Hz) to mimic natural brain activity (i.e., endogenous theta oscillations). In general, intermittent TBS protocols are believed to increase cortical excitability, whereas continuous TBS protocols are believed to reduce activity in the target region (Brunoni et al., 2019).

In psychiatry, NIBS techniques which target the DLPFC have been shown to produce reliable and lasting antidepressant effects in clinical samples with depression (Brunoni et al., 2017), and evidence for therapeutic effects in other psychiatric disorders is rapidly increasing (Guo et al., 2017; Kekic et al., 2016). Moreover, studies in non-clinical samples have shown that NIBS targeting the DLPFC may improve attention control, as measured by classical tasks of executive functioning (Hauer et al., 2019; Sarkis et al., 2014). Given that AB may have a prominent role in perpetuating maladaptive emotion regulation, and the central role of the DLPFC, it is possible that the therapeutic effects associated with NIBS targeting the DLPFC may be related to mechanistic changes in AB.

2.2 Research questions

The current study aggregates existing published research findings from studies in healthy and psychiatric populations to examine the following questions using meta-analysis or, where insufficient data are available, narrative synthesis:

1) Is there an effect of NIBS targeting the left and/or right DLPFC on AB for emotional stimuli?

2) Is the effect of NIBS on emotional AB different for different NIBS techniques (i.e., tDCS, rTMS or TBS)?

3) Is the effect of stimulation on AB different for positive and negative emotional stimuli?

2.3 Methods

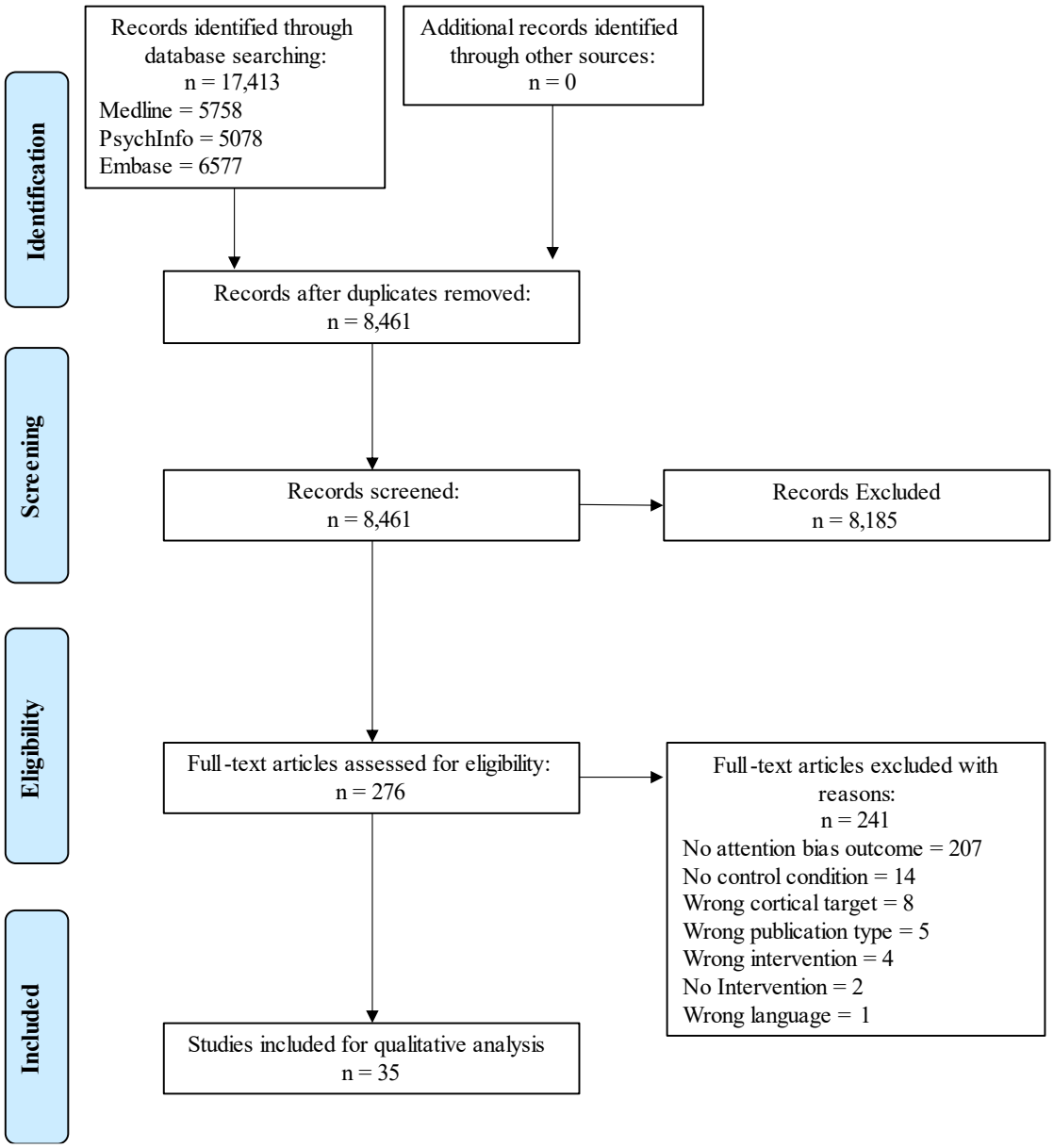
This review was pre-registered with the PROSPERO (reference: CRD42022369374) and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

2.3.1 Literature Review and Study Selection

Three electronic databases (MEDLINE, Embase, and PsycINFO) were searched (via OvidSP) from inception until 28th September 2022 using the search terms transcranial direct current stimulation, transcranial magnetic stimulation, or theta burst stimulation in combination with emotion, cognitive control, executive function*, attention, cognitive flexibility, affective flexibility, response inhibition, inhibitory control, Stroop, affective go, go/no-go, approach, avoid*, stop signal, or hot cognit*. Relevant database-specific terms (e.g., MESH terms) were used when applicable. Searches were limited to English and/or German language and to studies involving human participants. Reference lists of relevant articles and reviews were hand searched for additional articles; however, no additional articles were identified using this method.

Two authors (M.F. and A.H.) conducted the abstract and full-text review independently using an identical review protocol. The initial level of agreement between raters was high for both the abstract (intraclass correlation coefficient (ICC) = .879) and full-text review (ICC = .972). Any discrepancies during the full-text review were resolved by consensus. Suitable studies were selected for inclusion according to the following criteria; (1) adult human study population; (2) application of a single session of excitatory or inhibitory rTMS, tDCS or TBS targeting the DLPFC; (3) comparison of active stimulation to sham stimulation or stimulation of a control site (e.g., the vertex); (4) inclusion of at least one task measure of emotional AB. Emotional AB was defined as the selective attention towards emotional stimuli of any valence. As such, suitable paradigms for outcome measure assessment included (but were not limited to) go/no-go, Stroop, dot-probe and attention engagement/disengagement tasks using emotional stimuli (e.g., emotional images, images of emotive faces, or emotionally salient words). All papers that did not meet the inclusion criteria were excluded, with the reasons documented (see Figure 2.1).

Figure 2.1. PRISMA Flow Diagram



2.3.2 Assessment of Bias

Methodological quality was coded independently (M.F., L.H., M.A., and B.I.) using the Cochrane risk of bias assessment tool. The initial level of agreement between raters was high (87%). Discrepancies were resolved by discussion, in which a consensus rating was assigned. Ratings of “low”, “high”, and “some concerns” were assigned to each dimension based on the criteria outlined by the Cochrane Collaboration (Higgins et al., 2011).

2.3.3 Data extraction

Two reviewers (B.D. and M.F.) extracted data from all included studies into an electronic summary table, which was then checked by two other reviewers (A.H. and L.R.). Data extracted included sample size, participant characteristics (age, % female), type of stimulation (rTMS, tDCS or TBS), lateralisation, localisation method, sham methodology or control site, stimulation duration, stimulation protocol (e.g., excitatory or inhibitory stimulation, stimulation intensity, electrode placement for tDCS, and number of pulses for rTMS and TBS) and factors related to the outcome measures (e.g., stimuli used, assessment paradigm) and relevant statistics (i.e., mean, standard deviations (SD), *F*-value, *T*-value). A plot digitiser program (Rohatgi, 2017) was used to estimate means and SD when data was available in chart form only. When SD was not reported, it was estimated from standard error (*SE*) using the equation $SD = SE \times \sqrt{n}$.

2.3.4 Effect size calculation

Effect sizes were coded such that negative effect sizes reflect reduced AB following active stimulation. When applicable, the correlation between outcome measures for repeated measure study designs was imputed using the paired sample T-statistic and formulas outlined in Morris and DeShon (2002); the formula $T = \sqrt{F}$ was used to estimate the paired T-test statistic from the one-way analysis of variance (ANOVA) F-statistic (Lipsey and Wilson, 2001). Otherwise, a default correlation of .5 was imputed. This approach provides a conservative estimate of effect size without ignoring within-subject aspects of the study design (Follmann et al., 1992).

If multiple studies were published using the same participants, to prevent homogeneity inflation due to correlated data, only the study with the largest sample was included in the analyses. In studies that administered more than one relevant outcome measure to the same participants, effect sizes were averaged across outcomes to create a study-specific composite score and the variance was calculated using the method outlined by Borenstein, Hedges, Higgins & Rothenstein (2009). If studies used multiple active stimulation groups (e.g., clinical and non-clinical groups), each independent study-subgroup was treated as a separate study for all data analyses. This resulted in a single effect size estimate for each study and/or independent study-subgroup for each meta-analysis.

2.3.5 Procedure

We conducted a meta-analysis of studies using unilateral stimulation to increase cortical excitability (i.e., anodal tDCS, high frequency rTMS, and intermittent theta burst stimulation; number of studies (*k*) = 22) at the left and right DLPFC respectively. A meta-analysis of studies using bilateral tDCS to simultaneously excite and inhibit DLPFC activity was also conducted (*k* = 6). As there were too few studies utilising cathodal tDCS (*k* = 2), low frequency rTMS (*k* = 3) or continuous TBS (cTBS; *k* = 2), findings pertaining to these studies were evaluated using narrative synthesis.

2.3.6 Statistical Analyses

Statistical analyses were conducted using STATA (StataCorp, 2017) '*metan'* command. Sub-group analyses were then conducted to assess the effect of each stimulation technique ('*subgroup(technique*)). Prior to analyses, effect size data for individual studies were inspected for extreme outliers (±3 SDs from the mean effect size across studies) however, none were identified. Heterogeneity was suspected a priori, therefore random-effects meta-analysis was used (Hedges & Vevea, 1998). The standardised mean difference was used in this meta-analysis as a summary statistic. The standardised mean difference expresses the size of the exposure effect in each study relative to the variability observed in that study. Here, the standardised mean difference has been reported as Hedge's g, as this transformation corrects for effect size inflation in studies with small sample sizes (Hedges & Olkin, 2014).

Where a significant overall effect is observed, meta-regression was used to examine the effect of study design and sample characteristics on emotional AB ('*metareg'* command). Here, predictors included mean age, percentage female participants, control condition (sham vs active control), study design (within vs between subjects) and mode of stimulation delivery (online vs offline). Homogeneity of the effect size was assessed using the Q statistic, and further quantified using the I^2 statistic. I^2 calculates the percentage of the between-study variability that is attributable to true heterogeneity between studies, rather than random sampling error. The I^2 statistic is conventionally interpreted as follows: small <25%, moderate 25–50%, large >50%; (Huedo-Medina et al., 2006). Publication bias was initially assessed via visual inspection of the funnel plot, and further quantified using the Egger regression test for funnel plot asymmetry (Egger et al., 1997).

2.4 Results

A total of 35 (22 tDCS; 10 rTMS; 3 TBS) studies incorporating data from 37 different study populations met the inclusion criteria (i.e., two studies reported on independent clinical and non-clinical samples). Of these, data for meta-analysis were available from 32 studies, 22 using tDCS, 9 using rTMS and 1 using TBS. This represents data from 1,532 participants (67.3% female) with an average age of 26.4 years. Most studies used healthy volunteers (k = 25), although seven studies were conducted in clinical samples with mood (k = 4), anxiety (k = 3) or substance use disorders (k = 1), and four studies used healthy populations with elevated symptoms of psychopathology (e.g., low mood or trait anxiety).

Among the included articles, two used both inhibitory and excitatory protocols (Heeren, et al., 2015; Pecchinenda, et al., 2015) and seven assessed the effects of stimulation on both the left and right DLPFC (Aboulafia-Brakha et al., 2016; Bermpohl et al., 2005, 2006; De Raedt et al., 2010; Leyman et al., 2009; Sanchez-Lopez et al., 2018; Tupak et al., 2013). Additionally, five studies examined the effects of bilateral stimulation of the DLPFC (Brunoni et al., 2014; Ironside, et al., 2016; Kelley & Schmeichel, 2016; Liu et al., 2022; Sagliano, et al., 2017) or bilateral stimulation involving the left DLPFC (Nejati et al., 2021; Nejati et al., 2022). Finally, 19 studies assessed the effect of stimulation on AB for negative stimuli, whereas 11 studies assessed the effect of stimulation on AB for positive stimuli. Study characteristics, including their key findings relating to emotional AB, are summarised in Table 2.3 and Table 2.4 for studies using unilateral and bilateral tDCS. For studies using rTMS and TBS, study characteristics are presented in Table 2.5 and Table 2.7.

Excitatory stimulation of the left DLPFC and emotional AB

We identified 22 studies of emotional AB that used unilateral stimulation to increase cortical excitability at the left DLPFC (i.e., using anodal tDCS, HD-tDCS, HF rTMS, or iTBS). Meta-analytic and heterogeneity statistics, and results pertaining to publication bias are presented in Table 2.1.

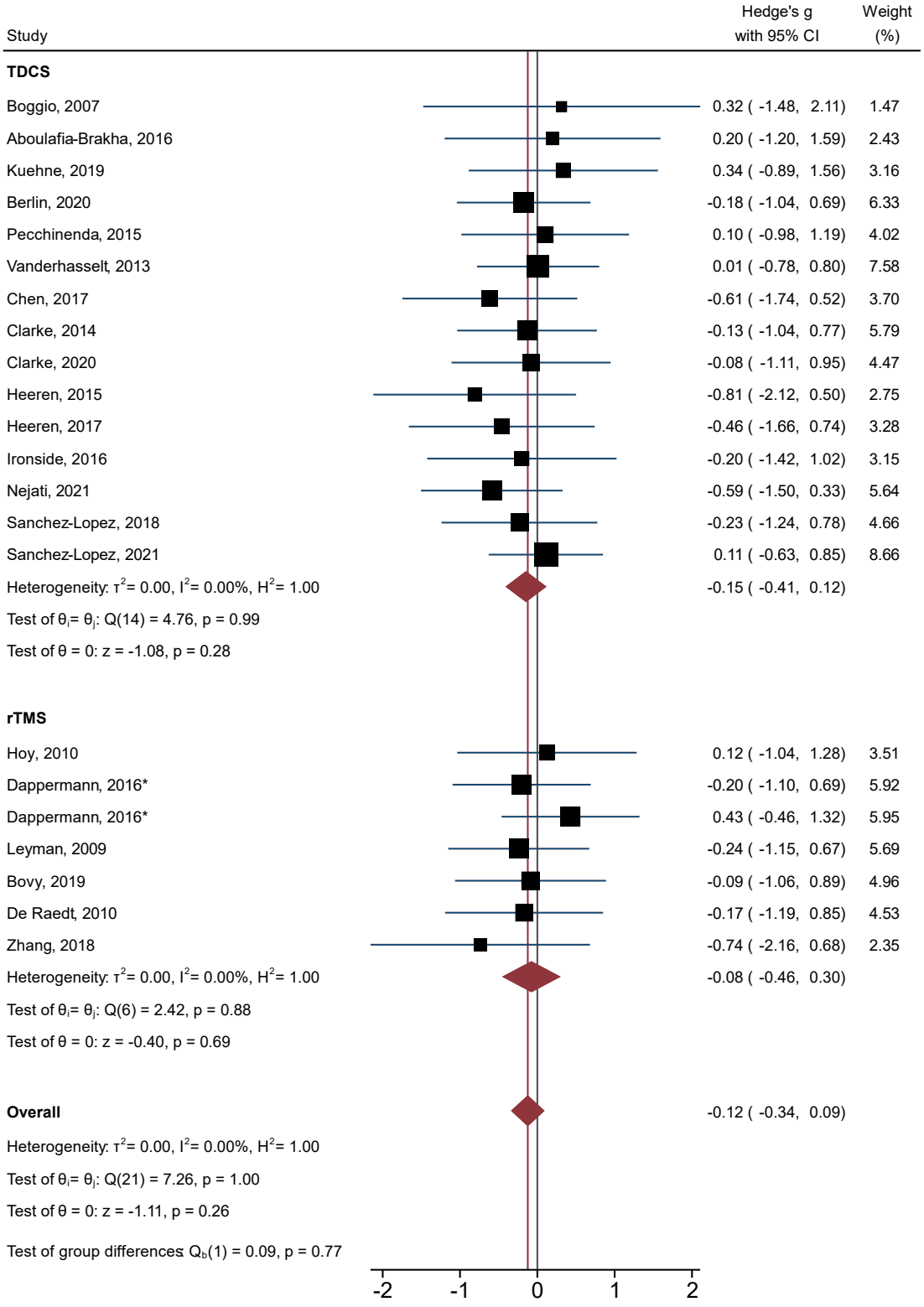
Random-effects meta-analysis indicated that, overall, unilateral excitation of the left DLPFC had no significant effect on emotional AB (g = -.124, p = .625). Similarly, sub-group analysis which distinguished between tDCS and rTMS techniques yielded no significant effect for stimulation on attention control. See Figure 2.2 for a forest plot summary of individual study effect sizes and confidence intervals. Additionally, random-effects meta-analysis indicated that upregulation of the left DLPFC had no significant effect on AB for negative (g = -.171, p = .170) or positive (g = -.042, p = .813) stimuli (see Appendix A.1 and Appendix A.2 for forest plot summaries). Overall, heterogeneity was similar across studies (Q = 7.27, p = .998, I^2 = 0) and the funnel plot of effect sizes by standard error (Figure 2.3) was relatively symmetrical, suggesting low risk for publication bias. Egger's test confirmed this (p = .628).

Table 2.1. Meta-analytic results by technique and valence for studies of excitatory left DLPFC stimulation.

	N	*K*	Meta Analytic Effect Size					Homogeneity			*p* Egger's
			G	*SE*	*LL*	*UL*	*P*	*Q*	*P*	I^2	
Overall	939	22	-.124	.111	-.311	.094	.265	7.26	.998	0	.628
Technique											
tDCS	688	15	-.147	.135	-.412	.119	.273	4.76	.989	0	
rTMS	251	7	-.077	.133	-.456	.302	.691	2.42	.878	0	
Valence											
Negative	804	19	-.171	.125	-.416	.073	.170	7.33	.987	0	.758
Positive	449	11	-.041	.175	-.384	.302	.813	2.09	1.00	0	.628

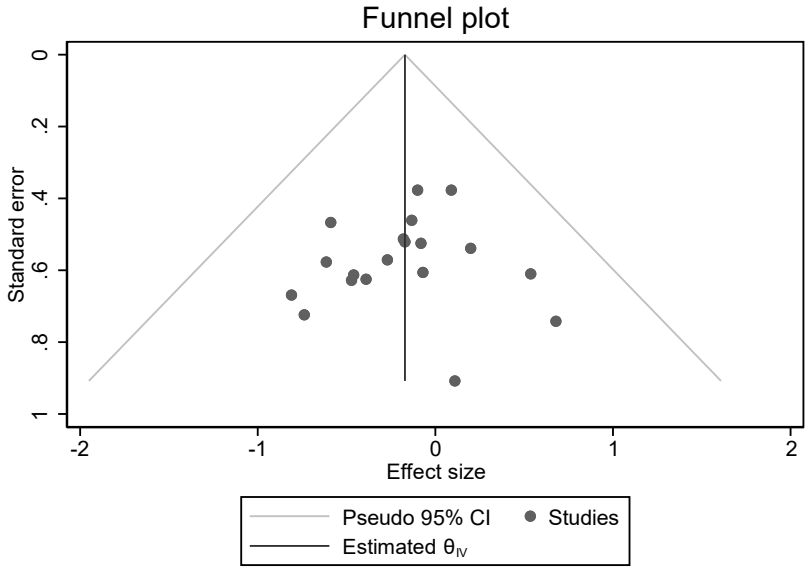
N, sample size, K, number of studies; G, Hedge's g (effect size); SE, standard error; LL, lower limit; UL, upper limit; P, probability (p) value; Q, Cochrane's Q which tests whether effect sizes follow a chi-square distribution; I^2, I^2 index showing percentage variability accounted for by true heterogeneity.

Figure 2.2. Forest plot showing the effect of unilateral excitation of the left DLPFC on emotional AB.



* Two independent effect sizes are reported for Dappermann et al. 2016 (the upper relates to the effect in participants with spider phobia, and the lower relates to the effect in healthy adults.

Figure 2.3. Funnel plot of effect sizes by standard error for studies of the effect of unilateral excitation of the left DLPFC on emotional AB.



2.4.1 Excitatory stimulation of the right DLPFC and emotional AB

We identified 7 studies of emotional AB that used unilateral stimulation to increase cortical excitability at the right DLPFC. Meta-analytic and heterogeneity statistics, and results pertaining to publication bias are presented in Table 2.2.

Data from 7 studies were used in a meta-analysis of the effect of unilateral excitation of the right DLPFC on emotional AB. Results indicated that there was no overall effect for right DLPFC stimulation on emotional attention control (g = .246, *p* = .149). Similarly, sub-group analyses revealed that neither tDCS (k = 4, g = .170, p = .449) nor rTMS (k = 3, g = .347, *p* = .183) significantly influenced attention for emotional stimuli. Similarly, the random-effects meta-analysis revealed no valence-specific significant effect for right DLPFC stimulation on AB (negative: *g* = .343, *p* = .135; positive: *g* = .175, *p* = .484; see Appendix A.3 and Appendix A.4 for forest plot summaries). Overall effect sizes for individual studies and confidence intervals are summarised in Figure 2.4. Heterogeneity was similar across studies (Q = 3.12, *p* = .792, I^2 = 0). The funnel plot of effect sizes by standard error (Figure 2.5) showed some asymmetry, suggesting risk for publication bias, however, results of the Eggers test revealed that risk is low (*p* = .163).

Table 2.2. Meta-analytic results by technique and valence for studies of excitatory right DLPFC stimulation.

	N	*K*	Meta Analytic Effect Size					Homogeneity			*p* Egger's
			G	*SE*	*LL*	*UL*	*P*	*Q*	*P*	I^2	
Overall	251	7	.246	.170	-.088	.579	.149	3.12	.792	0	.163
Technique											
tDCS	164	4	.170	.225	-.270	.610	.449	2.71	.439	0	
rTMS	87	3	.347	.261	-.164	.859	.183	.144	.934	0	
Valence											
Negative	169	5	.343	.229	-.107	.792	.135	1.31	.863	0	.348
Positive	141	4	.175	.230	-.315	.664	.484	1.52	.676	0	.761

N, sample size, K, number of studies; G, Hedge's g (effect size); SE, standard error; LL, lower limit; UL, upper limit; P, probability (p) value; Q, Cochrane's Q which tests whether effect sizes follow a chi-square distribution; I^2, I^2 index showing percentage variability accounted for by true heterogeneity.

Figure 2.4. Forest plot showing the effect of unilateral excitation of the right DLPFC on emotional AB.

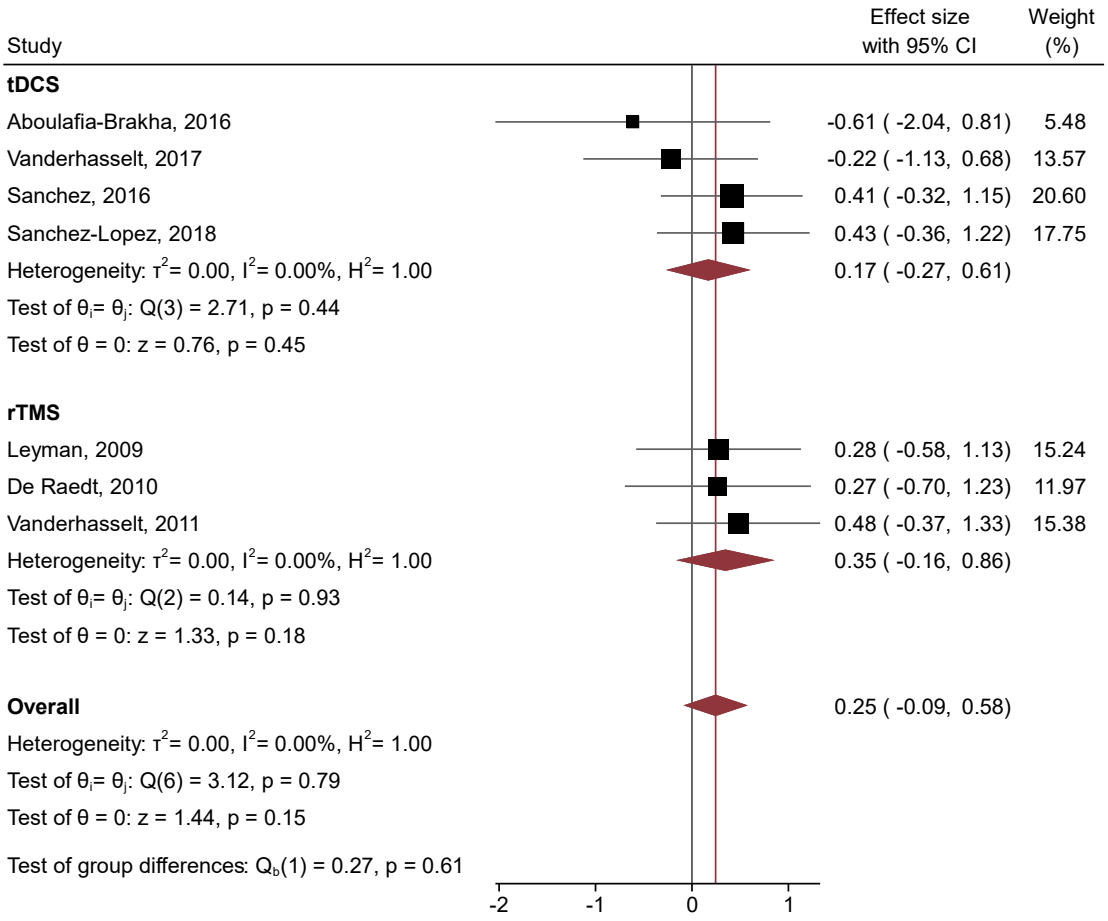
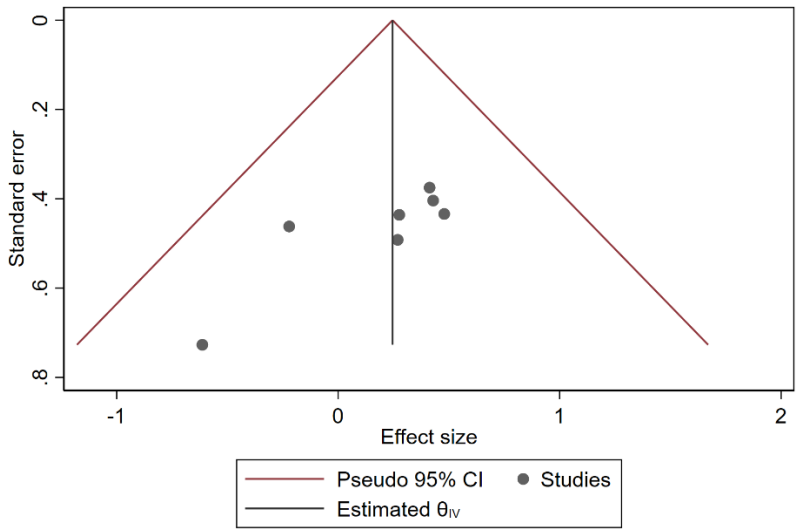


Figure 2.5. Funnel plot of effect sizes by standard error for studies of the effect of unilateral excitation of the right DLPFC on emotional AB.



2.4.2 Inhibitory stimulation of the left DLPFC and emotional AB

We identified five studies that used unilateral stimulation to reduce cortical excitability at the left DLPFC (i.e., using cathodal tDCS, LF rTMS, or continuous TBS). However, as data were not available from one of these studies (Tupak et al., 2013) it was not possible to evaluate the effect of stimulation on AB using meta-analysis, so a narrative synthesis of study findings is presented.

Overall, findings relating to the effect of inhibitory stimulation of the left DLPFC were highly varied. Two studies applied cathodal tDCS over the left DLPFC. First, Pecchinenda et al. (2015) assessed emotional AB in 45 healthy adults using a face-word interference task. The authors reported that cathodal stimulation of the right DLPFC reduced interference for positive, but not negative, facial expressions, suggesting a reduced AB towards positive emotion. Similarly, Heeren et al. (2015) reported that stimulation did not alter AB towards threat in adults with high levels of trait anxiety, as measured using a dot-probe paradigm with negative emotional facial expressions (disgust). In contrast, studies using rTMS reported poorer performance on affective go/no-go tasks for trials involving both positive and negative emotional stimuli following low-frequency stimulation of the left DLPFC (Bermpohl et al., 2005, 2006), although in Bermpohl et al. (2006), this disruptive effect was only observed in participants with mild, as opposed to moderate-severe, depressive symptoms. One study

has used continuous TBS to reduce left DLPFC excitability (Tupak et al., 2013) however, no effect for stimulation was observed.

2.4.3 Inhibitory stimulation of the right DLPFC and emotional AB

Similarly, few studies have evaluated the effect of inhibitory stimulation of the right DLPFC on emotional AB ($k = 4$), so it was not appropriate to evaluate the effect of stimulation on AB using meta-analysis. Overall, findings have been highly variable, with 50% of studies reporting no effect of stimulation on emotional AB (Bermpohl et al., 2005; Tupak et al., 2013). For example, one study reported significant reductions in AB for fearful faces in eight healthy participants following low frequency rTMS (van Honk et al., 2002), whereas another found no significant effect of low-frequency rTMS on affective go/no-go task performance in 11 healthy participants (Bermphol et al., 2005). In line with this, Bermpohl et al. (2006) found that low-frequency rTMS improved affective go/no-go performance in 10 participants with an acute depressive episode, but this beneficial effect declined with decreasing depression severity and tended to reverse for the eight partially or completely remitted participants.

2.4.4 Bilateral stimulation of the DLPFC and emotional AB

Five studies examined the effect of bilateral tDCS targeting the DLPFC. During bilateral tDCS, anodal and cathodal tDCS are delivered simultaneously to different cortical targets. Included studies assessed the effect of an anode left/cathode right montage, and data relating to this montage were used in a random-effects meta-analysis of effect sizes. Results indicated that bilateral stimulation had no significant overall effect on emotional AB (g = -0.318, $p = .139$). See Figure 2.6 for a forest plot summary of individual study effect sizes and confidence intervals. Similarly, the anode left/cathode right montage was not associate with any significant overall effect on negative (-0.368, $p = .115$) or positive AB ($g = -0.031$, $p = 0.932$; see Appendix A.5 and Appendix A.6 for forest plot summaries). Overall, heterogeneity was similar across studies ($Q = 3.06$, $p = .551$, $I^2 = 0$) and the funnel plot off effect sizes by standard error (Figure 2.7) was of moderate symmetry, suggesting low risk for publication bias. The results of the Eggers test for funnel plot asymmetry confirmed this ($p = .242$).

Additionally, two studies examined the effect of the inverse electrode placement (i.e., anode right/cathode left; AR/CL) on AB (Kelley & Schmeichel, 2016; Sagliano et al., 2017). Both studies reported that AR/CL tDCS was associated with significant reductions in emotional AB with large effect sizes. First, Kelley and Schmeichel (2016) reported that AR/CL tDCS, and not AL/CR tDCS stimulation or sham, reduced AB to both positive and negative emotional stimuli, as demonstrated by faster reaction times on an emotional approach/avoidance task (Kelley & Schmeichel, 2016). Second, Sagliano et al. (2017) observed faster disengagement with threatening images after AR/CL tDCS, as opposed to AL/CR tDCS or sham, indicating reduced threat-related AB. Relatedly, two studies have assessed the effect of bilateral montages involving the left DLPFC and the ventromedial prefrontal cortex (VMPFC) (Nejati et al., 2021; Nejati et al., 2022) however, findings have been mixed. One study reported that simultaneous anodal stimulation of the left DLPFC and cathodal stimulation of the right VMPFC, relative to the inverse electrode arrangement and sham, was associated with reduced interference by emotional stimuli, regardless of valence, during the emotional Stroop task and the affective go/no-go task. However, in a later study using a visual probe paradigm, no effect for either montage was observed.

Figure 2.6. Forest plot showing the effect of bilateral tDCS using the anode left/cathode right electrode montage on emotional AB.

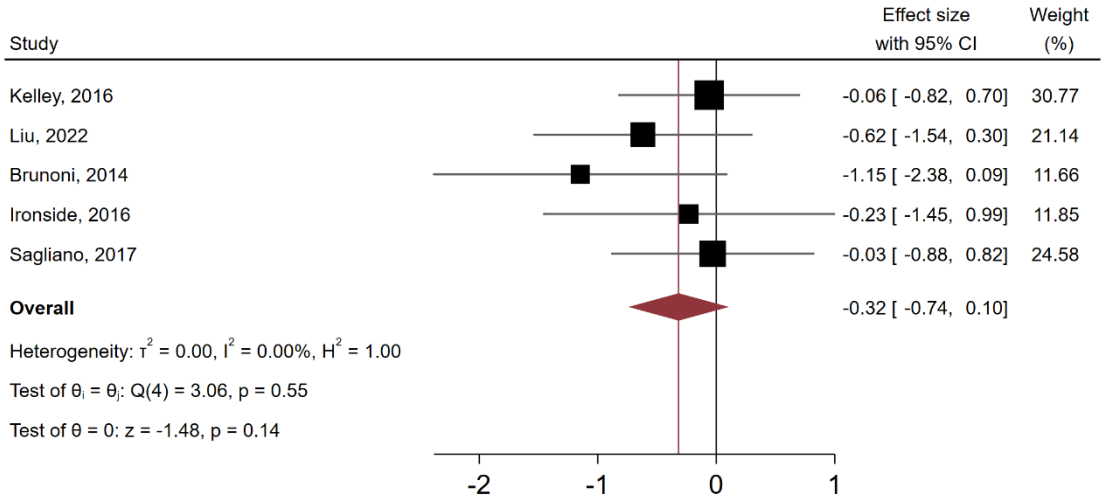


Figure 2.7. Funnel plot of effect sizes by standard error for studies of the effect of bilateral tDCS (anode left/cathode right montage) on emotional AB.

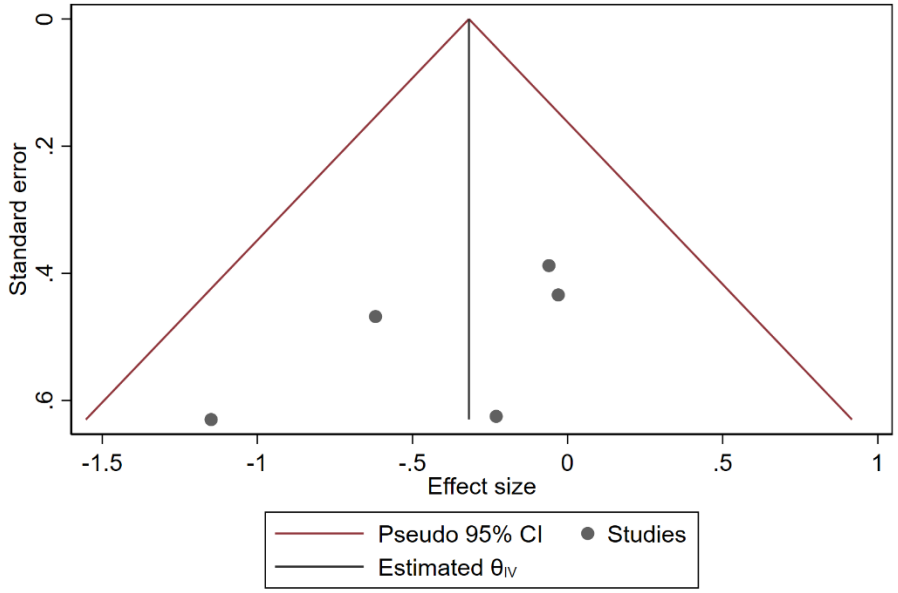


Table 2.3. Study characteristics for studies using anodal and/or cathodal tDCS protocols.

Study	Sample	Design	N (% F)	Age (M, SD)	Target	Control	Protocol	Parameters	Task	Stimuli	Valence	Findings
Aboulafia-Brakha et al. 2016	Healthy	Single-blind non-randomised controlled trial (3 arms)	45 (53.0)	27.2 (6.7)	Left & Right $DLPFC_1$	30s active stimulation	Anodal	25 mins, 1.5mA. Reference electrode over contralateral supra orbital area. Task administered simultaneously.	Affective Switch Task	Faces	Positive, Negative	Right DLPFC tDCS reduced switch-costs for emotion. Left DLPFC tDCS reduced switch costs for gender.
Berlin et al. 2020	Healthy	Single-blind randomised controlled trial (2 arms)	44 (74.5)	28.1 (11.7)	Left $DLPFC_1$	30s active stimulation	Anodal	30 mins, 1.0 mA, 30s face in/out. Reference electrode over the trapezius muscle.	Emotional Stroop Task	Words	Positive, Negative, Neutral	No effect for left DLPFC tDCS on interference by emotional stimuli.
Boggio et al. 2007	Depression	Double-blind randomised controlled trial (3 parallel arms)	26 (62.2)	48.7 (7.5)	Left $DLPFC_1$	(1) Occipital cortex tDCS (2) 30s active stimulation	Anodal	20 mins, 2 mA. Reference electrode over right supra orbital area.	Affective go/no-go	Scenes	Positive, Negative	Left DLPFC tDCS improved task accuracy during positive, but not negative, trials.
Chen et al. 2017	Healthy	Single-blind randomised controlled trial (2 parallel arms)	50 (68.0)	19.6 (3.3)	Left $DLPFC_1$	20s active stimulation	Anodal	2mA, 20 mins, 30s face in/out. Reference electrode over trapezius muscle.	Dual-Video Stressor Task	Scenes	Positive, Negative	AB for threat was attenuated by left DLPFC tDCS but not sham.
Clarke et al. 2014	Healthy	Single-blind randomised controlled trial (4 parallel arms)	77 (63.6)	20.0 (9.3)	Left $DLPFC_1$	60s active stimulation	Anodal	1mA, 30s face in/out for task duration (~17 minutes). Reference electrode over trapezius muscle. Simultaneous ABMT: 50% trained to attend, 50% trained to avoid.	Dot Probe Task	Words	Negative, Neutral	Left DLPFC tDCS associated with greater AB acquisition in the targeted direction (toward or away from threat) than sham.
Clarke et al. 2020	Healthy	Single-blind randomised controlled trial (4 parallel arms)	116 (69.0)	23.0 (7.4)	Left $DLPFC_1$	60s active stimulation	Anodal	2mA, 20 min, 60s face in/out. Reference electrode over trapezius. Simultaneous directed emotion regulation task (directed to down regulate or maintain emotion).	Dot Probe Task	Words	Negative, Neutral	No effect for left DLPFC tDCS on AB to threat regardless of whether participants were directed to down-regulate or maintain their emotions.
Heeren et al. 2015	High trait anxiety	Double-blind randomised controlled trial (3 parallel arms)	56 (100)	19.9 (1.8)	Left $DLPFC_1$	30s active stimulation	Anodal & Cathodal	2mA, 20 minutes, 30s face in/out. Reference electrode over the right supra orbital area. Simultaneous administration of ABMT.	Dot Probe Task	Faces	Negative, Neutral	Anodal tDCS, but not cathodal tDCS or sham, with ABMT reduced total time gaze remains fixated on threat.
Heeren et al. 2017	Clinical (SAD)	Double-blind randomised crossover trial (2 arms)	19 (100)	24.2 (4.9)	Left $DLPFC_1$	30s active stimulation	Anodal	2mA, 25 mins, 30s face in/out. Reference electrode over right shoulder. Simultaneous task administration.	Dot Probe Task	Faces	Negative, Neutral	Left DLPFC tDCS, but not sham, was associated with reduce AB to threat.

Continued over page.

Table 2.3 Study characteristics for studies using anodal and/or cathodal tDCS protocols (continued).

Study	Sample	Design	N (% F)	Age (M, SD)	Target	Control	Protocol	Parameters	Task	Stimuli	Valence	Findings
Ironside et al. 2016	Healthy	Double-blind randomised controlled trial (3 arms)	60 (100)	24.7 (3.9)	$DLPFC_1$	NR	Anodal & Bilateral	20min, 2mA. (a) AL/CR, (b) Anode left DLPFC /cathode right supra orbital area.	Dot Probe Task	Faces	Positive, Negative	AL/CR tDCS reduced AB to threat relative to anodal left DLPFC tDCS and sham.
Kuehne et al. 2019	Healthy	Single-blind pseudorandomised crossover trial (2 arms)	18 (50.5)	24.0 (2.6)	Left $DLPFC_1$	30s active stimulation	HD-tDCS	HD-tDCS, reference electrodes at positions Fz, C3, FP1 & F7. 20 mins, 0.5mA, 5s face in/out.	Emotional Stroop Task	Faces with words	Positive, Negative	Left DLPFC tDCS increased emotional interference effect.
Nejati et al. 2021	Clinical (GAD)	Single-blind randomised crossover trial (5 arms)	34 (63.3)	20.3 (6.5)	DLPFC & $VMPFC_1$	30s active stimulation	Arms 1 & 2: Anodal Arms 3 & 4: Bilateral	(1) anode left DLPFC /cathode VMPFC, (2) anode VMPFC / cathode DLPFC, (3) anode left DLPFC, (4) anode VMPFC (reference left shoulder). 20 min, 1.5mA, 30s fade in/out.	Dot Probe Task	Faces	Negative, Neutral	Anodal VMPFC and anodal DLPFC stimulation reduced AB to threat relative to sham. No effect for bilateral stimulation montages.
Pecchinenda et al. 2015	Healthy	Single-blind randomised controlled trial (3 arms)	43 (76.7)	23.0 (3.2)	Left $DLPFC_1$	30s active stimulation	Anodal & Cathodal	15 mins, 1.5 mA, 30s face in/out. Reference electrode over contralateral supra orbital area. Concurrent task administered.	Face-Word Task	Faces with words	Positive, Negative	Anodal, but not cathodal, left DLPFC tDCS reduced emotional interference relative to sham.
Sanchez et al. 2016	Healthy	Single-blind randomised crossover trial (2 arms)	30 (66.7)	23.3 (4.2)	Right $DLPFC_1$	15s active stimulation	Anodal	2mA, 20 mins, 15s face in/out. Reference electrode right supra orbital area.	Attention Engagement Disengagement	Faces	Positive, Negative, Neutral	Compared to sham stimulation, right DLPFC tDCS led to impairments in attentional disengagement from both positive and negative faces.
Sanchez-Lopez et al. 2018	Healthy	Single-blind randomised crossover trial (3 arms)	54 (59.3)	23.2 (NR)	Left & Right $DLPFC_1$	15s active stimulation	Anodal	2mA, 20 minutes, 30s face in/out. Reference electrode over the right supra orbital area.	Attention Engagement Disengagement	Faces	Positive, Negative, Neutral	Left DLPFC tDCS facilitated gaze disengagement, whereas right DLPFC tDCS increased difficulty disengaging from emotional faces.
Sanchez-Lopez et al. 2021	Low trait resilience	Single-blind randomised controlled trial (4 arms)	100 (77.0)	2.0 (4.3)	Left $DLPFC_1$	60s active stimulation	Anodal	2mA, 20 minutes, 30s face in/out. Reference electrode over the right supra orbital area. Simultaneous ABMT.	Attention Engagement Disengagement	Faces	Positive, Negative, Neutral	Real training + sham tDCS and real training + real tDCS both reduced AB for negative stimuli.
Vanderhasselt et al. 2013	Healthy	Single-blind crossover trial (2 arms)	25 (NR)	22.1 (3.8)	Left $DLPFC_1$	20s active stimulation	Anodal	20 mins, 2mA, 20s face in/out.	Cued Emotional Control Task	Words, Faces	Positive, Negative	No effect for left DLPFC tDCS on interference by emotional stimuli.
Vanderhasselt et al. 2017	Healthy	Single-blind counter-balanced crossover trial (2 arms)	35 (66.8)	23.4 (4.4)	Right $DLPFC_1$	15s active stimulation	Anodal	20mins, 2 mA, 15s face in/out.	Cued Emotional Control Task	Words, Faces	Positive, Negative	Right DLPFC tDCS improved emotional interference control among participants with high trait rumination relative to sham.

Note: target located using the 10-20 EEG system[1], Abbreviations: AB, attention bias, *ABMT, attention bias modification training; AL/CR, anode left/cathode right; DLPFC, dorsolateral prefrontal cortex; F, female; GAD, generalised anxiety disorder mA, milliamps; NR, not reported; SAD, social anxiety disorder; tDCS, transcranial direct current stimulation*

Table 2.4 Study characteristics for studies using bilateral tDCS protocols

Study	Population	Design	N (% F)	Age (M, SD)	Target	Control	Protocol	Parameters	Task	Stimuli	Valence	Finding
Brunoni et al. 2014	Depression	Double-blind randomised controlled trial (2 arms)	24 (50.0)	38.5 (10.9)	$DLPFC_2$	60s active stimulation	Bilateral	AL/CR. 225 mins, 2mA, 5s face in/out. Task administered simultaneously.	Emotional Stroop Task	Words	Positive, Negative, Neutral	Active, but not sham, DLPFC tDCS reduced interference effect for negative words.
Ironside et al. 2016	Healthy	Double-blind randomised controlled trial (3 arms)	60 (100)	24.7 (3.9)	$DLPFC_1$	NR	Anodal & Bilateral	20min, 2mA. (a) AL/CR, (b) Anode left DLPFC/cathode over right supra orbital area.	Dot Probe Task	Faces	Positive, Negative	AL/CR tDCS reduced AB to threat relative to anodal left DLPFC tDCS and sham.
Kelley & Schmeichel 2016	Healthy	Double-blind randomised controlled trial (2 arms)	202 (53.9)	19.1 (1.5)	$DLPFC_1$	30s active stimulation	Bilateral	(1) AL/CR (2) AR/CL. 15 mins, 2mA, 5s face in/out.	Approach Avoidance Task	Words	Positive, Negative	AR/CL, and not AL/CR or sham, improved response inhibition, as demonstrated by reduced RTs for motive-incongruent responses.
Liu et al. 2022	Healthy	Single-blind randomised controlled trial (2 arms)	41 (65.1)	23.4 (1.1)	Left & Right $DLPFC_1$	30s active stimulation	Bilateral	AL/CR montage. 1.5mA, 20 mins, 15s fade in/out.	Emotional Oddball Task	Faces	Positive, Negative, Neutral	No significant effect for bilateral tDCS on accuracy or RTs.
Nejati et al. 2022	Depression	Single-blind counter-balanced crossover trial (3 arms)	20 (10.0)	30.4 (6.8)	DLPFC & $VMPFC_1$	30s active stimulation	Bilateral	(1) Anode left DLPFC / cathode VMPFC, (2) Anode VMPFC / cathode left DLPFC. 20 mins, 1.5mA, 30s face in/out. Task & tDCS completed concurrently.	Affective go/no-go & Emotional Stroop	Faces	Positive, Negative, Neutral	Anode left DLPFC/cathode right VMPFC reduced emotional AB, as demonstrated by fewer go/no-go errors and reduced interference during Stroop task performance.
Nejati et al. 2021	Clinical (GAD)	Single-blind randomised crossover trial (5 arms)	34 (63.3)	20.3 (6.5)	DLPFC & $VMPFC_1$	30s active stimulation	Arms 1 & 2: Bilateral Arms 3 & 4: Excitatory	(1) anode left DLPFC /cathode VMPFC, (2) anode VMPFC / cathode DLPFC, (3) anodal left DLPFC, (4) anodal VMPFC. 20 min, 1.5mA, 30s fade in/out.	Dot Probe Task	Faces	Negative, Neutral	Anodal VMPFC and anodal DLPFC stimulation reduced AB to threat relative to sham. No effect for bilateral stimulation.
Sagliano et al. 2017	Low and high trait anxiety	Single-blind counte-rbalanced crossover design (3 arms)	40 (100)	23.0 (0.5)	$DLPFC_1$	30s active stimulation	Bilateral	(a) AL/CR, (b) AR/CL. 1mA, 15 min, 20s face in/out.	Exogenous Cueing Task	Faces	Negative, Neutral	Low anxiety subjects: AR/CL tDCS increased difficulty disengaging from threat. High anxiety subjects: AR/CL tDCS increased threat detection (facilitation bias). No effect for AL/CR tDCS.

Note: target located using the 10-20 EEG system[1] or the '5-cm method' (Pascual-Leone et al., 1996)[2]. Abbreviations: AB, attention bias, AL/CR, anode left/cathode right; AR/CL, anode right/cathode left; DLPFC, dorsolateral prefrontal cortex; mA, milliamps; NR, not reported; RT, reaction time; tDCS, transcranial direct current stimulation; VMPFC, ventromedial prefrontal cortex.

Table 2.5 Study characteristics for studies using high and/or low frequency rTMS protocols.

Study	Sample	Design	N (%F)	Age (M, SD)	Target	Control	Frequency	Parameters	Task	Stimuli	Valence	Findings
Hoy et al. 2010	Healthy	Single-blind counter-balanced crossover trial (2 arms)	10 (60.0)	31.2 (7.7)	Left $DLPFC_1$	NR	HF	5 Hz, 120% rMT. 30 trains of 10s duration with 20s ITI (900 pulses, 15 mins). Concurrent viewing of emotional images.	AGNG	Words	Positive, Negative	No significant effect of rTMS (with or without positive affective priming) on emotional response inhibition.
Bermpohl et al. 2005	Healthy	Single-blind counter-balanced crossover trial (3 arms)	11 (54.0)	38.3 (13.9)	Left & Right $DLPFC_1$	Occipital cortex stimulation	LF	1 Hz stimulation at 60% maximum stimulator output for 10 minutes.	AGNG	Scenes	Positive, Negative	Left DLPFC rTMS significantly impaired task performance relative to right DLPFC and occipital rTMS.
Bermphol et al. 2006	Depression	Single-blind counter-balanced crossover trial (3 arms)	18 (61.0)	54.0 (9.0)	Left & Right $DLPFC_2$	Occipital cortex stimulation	LF	1 Hz stimulation at 60% maximum stimulator output for 10 minutes.	AGNG	Scenes	Positive, Negative	Right DLPFC rTMS improves task performance. Greater depression severity associated with greater improvement.
Leyman et al. 2009 (Exp. 1)	Healthy	Single-blind randomised crossover trial (2 arms)	22 (100)	24.0 (2.3)	Right $DLPFC_3$	Coil 90° angle resting on the scalp.	HF	10 Hz stimulation, 110% rMT. 40 trains of 3.9s duration with26.1s ITI (1560 pulses, 20 mins).	Negative Affective Priming	Faces	Positive, Negative	Right DLPFC rTMS associated with poorer emotional interference control.
Leyman et al. 2009 (Exp. 2)	Healthy	Single-blind randomised crossover trial (2 arms)	18 (100)	21.1 (1.45)	Left $DLPFC_3$	Coil 90° angle resting on the scalp.	HF	10 Hz stimulation, 110% rMT. 40 trains of 3.9s duration with26.1s ITI (1560 pulses, 20 mins).	Negative Affective Priming	Faces	Positive, Negative	No effect for left DLPFC rTMS on emotional interference control.
Mobius et al. 2017	Healthy	Single-blind counter-balanced crossover trial (2 arms)	23 (NR)	21.5 (3.0)	Left $DLPFC_1$	Coil 45° angle resting on the scalp.	HF	10 Hz stimulation, 110% rMT. 60 trains of 5s duration 25s ITI (3000 pulses, 30 mins).	Emotional Stroop	Faces	Negative, Neutral	No effect for left DLPFC rTMS on emotional interference control.
Zhang et al. 2018	Substance Abuse	Single-blind randomised controlled trial (2 parallel arms)	31 (0)	43.0 (9.2)	Left $DLPFC_2$	Coil at 90° angle resting on the scalp.	HF	10 Hz stimulation at 90% rMT. 40 trains of 5s and 10s ITI (2000 pulses, 10 mins).	Modified Affective Stroop	Scenes	Negative, Neutral	Left DLPFC rTMS, but not sham, reduced interference by emotional pictures. This pattern persisted to 2 weeks.
van Honk et al. 2002	Healthy	Single-blind counter-balanced crossover trial (2 arms)	20 (NR)	NR	Right $DLPFC_1$	Coil 90° angle resting on the scalp.	LF	1 Hz stimulation, 130% rMT. Stimulation duration NR.	Emotional Stroop	Faces	Negative, Neutral	Right DLPFC rTMS reduced interference by fearful faces (unmasked trials only).
Bovy et al. 2019	Healthy subjects with low mood	Single-blind randomised controlled trial (4 arms)	72 (34.9)	21.5 (2.97)	Left $DLPFC_1$	Coil at 45° angle resting on the scalp.	HF	10 Hz stimulation at 110% rMT. 30 trains of 5s duration with ITI of 25s (1500 pulses, 15 minutes). Active (50%) or sham (50%) ABMT during active/sham rTMS.	Dot Probe Task	Faces	Positive, Negative	No intervention yielded significant change in AB, and no significant between-group difference in AB.

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Table 2.6 Study characteristics for studies using high and/or low frequency rTMS protocols (continued).

Study	Sample	Design	N (%F)	Age (M, SD)	Target	Control	Frequency	Parameters	Task	Stimuli	Valence	Findings
De Raedt et al. 2010	Healthy	Single-blind randomised crossover trial (3 arms)	37 (100)	22.6 (2.6)	Left & Right $DLPFC_3$	Coil at 90° angle resting on the scalp.	HF	10 Hz stimulation at 110% rMT. 40 trains of 3.9s duration and 26.1s ITI (1560 pulses, 20 mins).	Exogenous Cueing Task	Faces	Negative, Neutral	Right DLPFC rTMS increased difficulty disengaging with angry faces. Left DLPFC rTMS diminished attentional engagement by angry faces.
Vanderhasselt et al. 2011	Healthy	Single-blind counter-balanced crossover trial (2 arms)	28 (100)	22.3 (2.6)	Right $DLPFC_3$	Coil at 90° angle resting on the scalp	HF	10 Hz stimulation at 110% rMT. 40 trains of 3.9s duration and 26.1 ITI (1560 pulses, 20 mins).	Exogenous Cueing Task	Faces	Negative, Neutral	Right DLPFC rTMS increased AB towards threatening information. AB acquisition was greater for subjects with higher trait anxiety scores.

Note: target located using the 10-20 EEG system[1], the '5-cm method' (Pascual-Leone et al., 1996)[2] or MRI-Guided Neuronagivation[3]. Abbreviations: AB, attention bias. DLPFC, dorsolateral prefrontal cortex; HF, high frequency; Hz, hertz; ITI, intertrain interval; LF, low frequency, rMT, resting motor threshold; NR, not reported; rTMS, repetitive transcranial stimulation.

Table 2.7 Study characteristics for studies using intermittent and/or continuous TBS protocols.

Study	Sample	Design	N (% F)	Age (M, SD)	Target	Control	Protocol	Parameters	Task	Stimuli	Valence	Finding
Deppermann et al. 2016	Spider Phobic & Healthy	Single-blind randomised controlled trial (4 parallel arms)	Phobic: 41 (53.0) Healthy: 42 (76.7)	Phobic: 27.5 (9.5) Healthy: 24.5 9 (7.4)	Left $DLPFC_1$	Coil at 90° angle resting on the scalp.	iTBS	40 trains (2s on, 8s off) of 10 triplet bursts (50 Hz), 80% rMT.	Emotional Stroop Task	Scenes	Positive, Negative, Neutral, Phobia	No effect for left DLPFC iTBS on emotional interference in either population.
Cao et al. 2018	Healthy	Single-blind randomised controlled trial (2 parallel arms)	25 (44.0)	23.3 (1.5)	Right PFC_1	Coil at 90° angle resting on the scalp.	cTBS	Triplet burst (50 Hz) every 200ms for 40s (600 pulses) at100% rMT.	Affective go/no-go	Faces	Positive, Negative, Neutral	No significant effect of cTBS over the right PFC on task performance.
Tupak et al. 2013	Healthy	Single-blind randomised controlled trial (3 arms)	51 (66.6)	23.1 (2.6)	Left & Right $DLPFC_1$	Coil at 45° angle resting on the scalp.	cTBS	Triplet burst (50 Hz) repeated every 200ms for 40s (600 pulses), 80% rMT.	Emotional Stroop Task	Words	Negative, Neutral	No effect for left or right DLPFC cTBS on emotional interference control.

Note: target located using the 10-20 EEG system[1]. Abbreviations: AB, attention bias, cTBS; continuous theta burst stimulation, DLPFC, dorsolateral prefrontal cortex; Hz, hertz; iTBS, intermittent theta burst stimulation; ITI, intertrain interval; NR, not reported; rMT, resting motor threshold; cTBS; continuous theta burst stimulation; iTBS, intermittent theta burst stimulation;

2.4.5 Risk of Bias Assessment

Outcomes from the Cochrane risk of bias tool for between-subjects and crossover designs are summarised in Figure 2.8 and Figure 2.9, respectively. Individual study ratings by domain are presented in Appendix A.7 and Appendix A.8. Overall, studies were rated as having low-to-moderate risk of bias, with the primary reason for concern relating to participant and personnel blinding. While the use of sham and control methodologies imply participant blinding, most studies failed to explicitly describe blinding procedures. Indeed, only 11.4% of studies reported that the personnel delivering stimulation were blind to active/sham allocation, and only one study reported that the person completing data analysis was blind to participant allocation. Moreover, few studies reported blinding success and several studies using a within-subject design reported high levels of participant drop out (defined as greater than 20%) between sessions (9.1%) which may be suggest poor quality blinding. While it can be challenging to blind the personnel administering stimulation, it can be accomplished with the use of the appropriate technology (e.g., a sham coil or code-operated tDCS equipment), and/or avoidance of within-subjects designs. The use of standardised protocols and scripts may also mitigate some of the bias associated with inadequate blinding of personnel.

Additionally, a heavy reliance on paradigms with well-documented psychometric limitations (e.g., emotional Stroop and visual probe without eye-tracking) raised concerns about bias during outcome measure assessment. Similarly, insufficient information was provided on participant drop out and/or missing data in 12.6% of studies, and only two studies provided sufficient information to assess risk of bias about how participants were allocated to a condition.

Finally, study quality would be improved by greater use of neuronavigation techniques for cortical target localisation; only 8.5% of studies used neuronavigation to identify the left or right DLPFC and, where neuronavigation was used, the DLPFC was identified using structural, as opposed to functional imaging co-ordinates. Studies using tDCS almost exclusively used the International 10-20 system to locate the DLPFC (95.4% of studies). In studies using rTMS, where neuronavigation was not used, studies located the cortical target using either the International 10-20 system (53.8%) or the “5-cm method” (23.1%) described by Pascual-Leone et al. (1996).

Figure 2.8. Cochrane risk of bias rating by domain for studies using a crossover design *(k* = 17) (percentage).

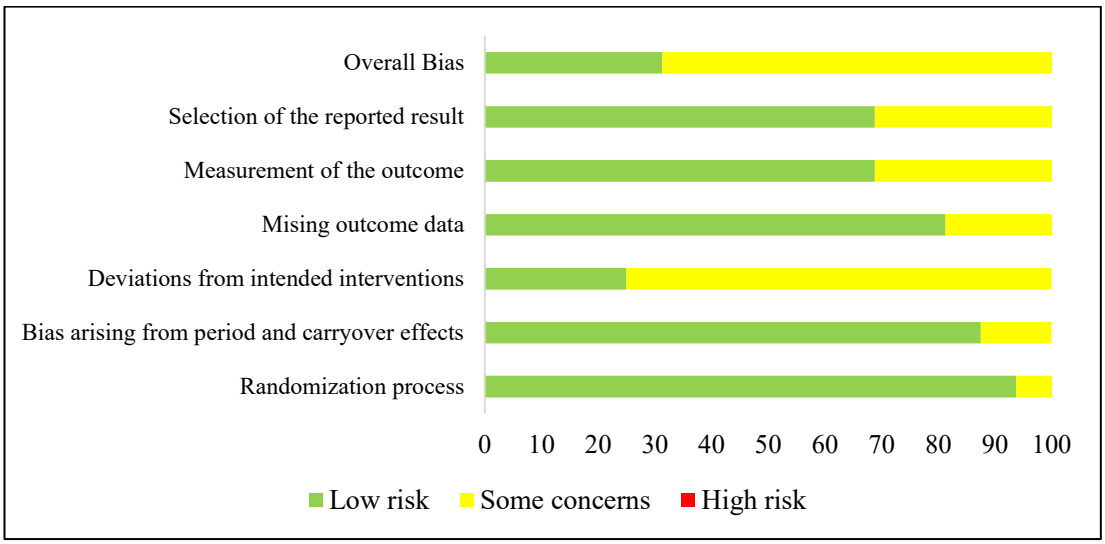
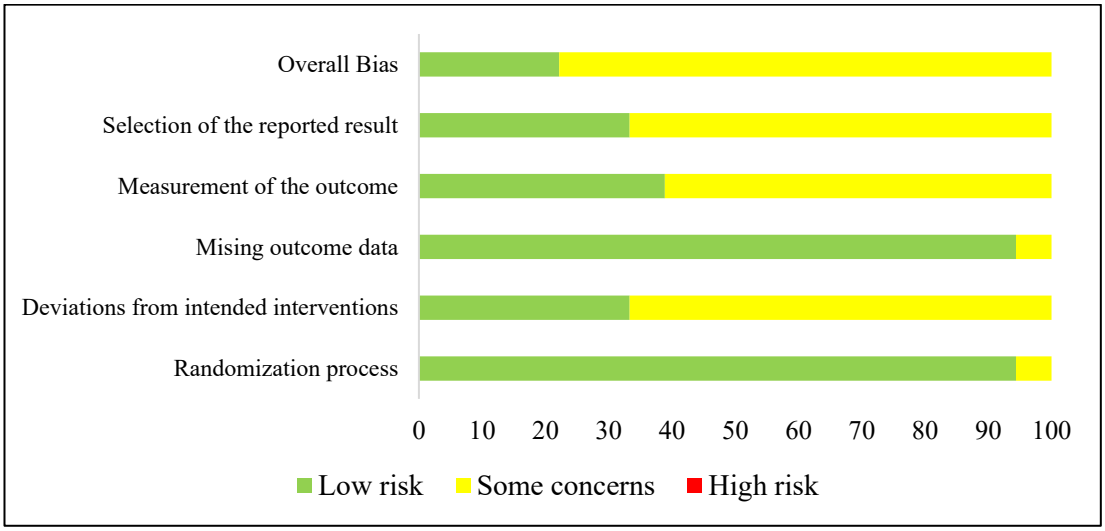


Figure 2.9. Cochrane risk of bias rating by domain for studies using a between-subjects (*k* = 18) design.



2.5 Discussion

This systematic review and meta-analysis collated findings from studies investigating the effects of NIBS targeting the left and/or right DLPFC on AB for emotional stimuli. Thus far, there is limited evidence to suggest that excitatory or inhibitory NIBS to the left or right DLPFC consistently alters emotional AB. Indeed, the results from our random effects meta-analyses revealed no significant effect for unilateral excitation of the left or right DLPFC on emotional AB overall, regardless of the NIBS technique applied. Similarly, no effect was observed for studies using a left anodal/right cathodal bilateral tDCS montage, suggesting that simultaneous excitation and inhibition of the left and right DLPFC, respectively, also did not effect emotional AB. Regarding unilateral inhibition of the DLPFC, findings from the small number of available studies were inconsistent and provided limited evidence for a reliable effect of stimulation on emotional AB.

This review and meta-analysis also found limited evidence to suggest that the effect of stimulation differed as a function of emotional valence. Meta-analyses revealed no significant effect for unilateral excitation of the left or right DLPFC on negative or positive AB specifically. Similarly, no significant effect for bilateral stimulation (anode left/cathode right) on AB for negative or positive emotion was observed. Comparatively few studies examined the effect of left or right DLPFC inhibition on negative or positive AB, and findings were highly variable, with some studies reporting no effect of stimulation on AB, and others reporting significant differences were associated with real vs sham stimulation. However, the direction of difference (i.e., increased or decreased AB) was inconsistent across studies.

There are a number of factors that may have contributed to null findings. For example, the effect of NIBS might only be detected in individuals with elevated baseline levels of AB. Emotional AB is elevated in populations with psychiatric illness, most notably major depression and anxiety disorders, however, only 12 of the included studies recruited participants with psychiatric disorder or elevated symptoms of psychopathology. Of interest, >80% of studies using clinical or subclinical samples found that NIBS was associated with significant change in AB for emotional stimuli. Indeed, findings in clinical and subclinical samples were generally consistent with the theorised effects; that is, that upregulation of the left DLPFC and down regulation of the right DLPFC would reduce AB towards

emotional stimuli (Bermpohl et al., 2006; Boggio et al., 2007; Brunoni et al., 2014; Heeren et al., 2015; Heeren et al., 2017; Nejati et al., 2021; Nejati et al., 2022; Zhang et al., 2018; but not Bovy et al., 2019; Dapperman et al., 2016), whereas down regulation of the left DLPFC and upregulation of the right DLPFC would increase AB towards emotional stimuli (Sagliano et al., 2017). In samples with anxiety and depression, unilateral downregulation of the left DLPFC was reported to have no effect on emotional AB (Bermphol et al., 2006; Heeren et al., 2015; Heeren et al., 2017) however, as emotional AB is a feature of disorders, it is possible that this reflects a ceiling effect. Indeed, inhibition of the left DLPFC was reported to exacerbate emotional AB in healthy samples (Bermphol et al., 2005). As such, more research in clinical and sub-clinical samples is needed to characterise the effect of NIBS on emotional AB.

The effect of a single session of NIBS may also be insufficient to alter AB. Indeed, there is extensive debate around the hypothesis that a single NIBS session can affect mood states and emotional processing in healthy participants or participants with a psychiatric disorder (see Remue, et al., 2016 for review). For example, Möbius et al. (2017) investigated whether a single session of high-frequency rTMS over the left DLPFC alters the effect of a negative mood induction procedure in 23 healthy participants. Here, the authors reported that mood was unchanged by rTMS only. Rather, mood decline only occurred in response to the mood induction procedure, and mood decline was more substantial when mood induction was preceded by real, as opposed to sham, rTMS. These findings were in line with the suggestion that a single session of rTMS does not change mood states in healthy individuals, but instead points to an interaction of rTMS, and potentially NIBS more broadly, and mood induction. In addition, it is plausible that non-significant findings in healthy populations indicate ceiling effects, as reported in other neuromodulation studies using emotional paradigms with healthy volunteers (e.g., Overman, et al., 2021). We recommend that future studies use a multi-session (e.g., 3 sessions) approach, either delivered as an accelerated (i.e., multiple sessions in one day) or traditional (i.e., one session per day) protocol, to more reliably measure the effects of NIBS on emotional AB.

Relatedly, studies included in this review used a wide range of stimulation protocols, and this introduces intervention-related methodological heterogeneity. Indeed,

stimulation protocol variability was substantial, even among those studies that used the same stimulation technique (e.g., rTMS). The effect of any neuromodulation technique is almost certainly dependent on the parameters used (e.g., session number and frequency, stimulation intensity, duration of stimulation, etc.), and yet no studies have examined whether the effect of stimulation on emotional AB (or emotions/attention more broadly) is different for different stimulation parameters. In the present review, the small number of studies precluded meaningful comparison between stimulation parameters, however, future research should aim to address this gap in the literature so that we might better characterise the effect of NIBS on emotional AB.

In a similar way, a wide range of outcome measures were used to assess emotional AB, and this introduces methodological heterogeneity. Moreover, several studies used outcome measures with poor psychometric properties. For example, the dot-probe paradigm was developed to address the shortcomings of the emotional Stroop task (i.e., the concern that the interference effect or delayed response latency observed during the emotional Stroop task might reflect attentional avoidance rather than attentional bias (De Ruiter & Brosschot, 1994). Accordingly, the dot-probe task enables differentiation between *vigilance* towards and *avoidance* of a given class of cues. However, serious issues with the dot-probe task have also been raised, including poor internal reliability and test-retest reliability (see Bar-Haim et al., 2007 for review). In response, a growing number of studies have applied eye-tracking paradigms, and studies have shown that eye-tracking methods may offer more reliable assessment of AB and provide greater insight into the components of biased attention (e.g., attention capture and disengagement) (Waechter et al., 2014). Indeed, free-viewing eye-tracking paradigms have received superior psychometric evaluations in both clinical (e.g., Soleymani, et al., 2020) and non-clinical populations (e.g., Veerapa et al., 2020). In the present review, only four studies used eye-tracking to evaluate emotional AB, and none used a free-viewing paradigm (Heeren et al., 2015; Sanchez-Lopez et al., 2021; Sanchez-Lopez et al., 2018; Sanchez et al., 2016). As such, we echo the suggestions of other researchers that, given their superior psychometric properties and ability to measure temporal dynamics of emotional AB, future studies use free-viewing eye-tracking paradigms to assess the effects of NIBS on emotional AB (Waechter et al., 2014).

The focus of this systematic review and meta-analysis is AB towards emotional stimuli, however, AB does not occur exclusively in the context of emotion and studies have shown that AB towards other salient stimuli may perpetuate maladaptive behaviours. Indeed, AB towards food cues, particularly high-calorie food cues, has been implicated in the maintenance of binge eating disorder (BED) (Appelhans et al., 2016; Brooks et al., 2011; Nijs & Franken, 2012; Stojek et al., 2018). Neuroimaging studies comparing individuals with BED to healthy controls (with and without obesity) suggest that people with BED show exaggerated activity in regions related to reward and emotion processing during food-cue exposure, as well as difficulties recruiting "top down" prefrontal resources in task measures of cognitive control (Balodis et al., 2015), and this is a probable driver of AB towards high-calorie food cues (Werthmann et al., 2019). Accordingly, AB towards high-calorie food cues has been identified as a candidate mechanistic target for intervention in eating and weight disorders. The present review found that neuromodulation may enhance control of attention in those with AB towards emotional stimuli at baseline, and it is possible that comparable ameliorating effects may be achieved in those with biases towards other salient stimuli, including high-calorie food cues. As such, neuromodulation may be a potent tool for treatment in obesity and BED. Indeed, a preliminary 10 session RCT of tDCS in adults with BED (n = 32) demonstrated that tDCS administration reduces AB towards high calorie food cues by post-treatment, and this reduction in AB towards high-calorie food cues endured to 45-day follow-up (Afzali et al., 2021).

To the best of our knowledge, this is the first meta-analytic review of the effect of NIBS on emotional AB. Our findings indicated that currently there is limited evidence to suggest that NIBS can alter emotional AB however, given the small number of highly heterogeneous studies available, this finding should be interpreted with caution. Future studies that investigate the effect of NIBS on emotional AB are encouraged but only those that address the methodological limitations to the current evidence. We recommend double-blind, randomised, sham-controlled trials that measure emotional attention bias using free-viewing eye-tracking in larger samples (e.g., >200).

Chapter 3. Food-related attention bias in obesity with and without binge eating disorder

Author contributions: The candidate designed the study with her supervisors, Professor Ulrike Schmidt and Professor Iain Campbell. The candidate obtained ethical approval from the King's College London Research Ethics Committee and the National Health Service (NHS) Research Ethics Committee and Health Research Authority. Recruitment and data collection were performed by the candidate (main contributor), Maaike Rae Boek and Katie Patterson. Data entry and statistical analyses were performed by the candidate. The candidate authored the chapter and received constructive feedback from her supervisors.

Abstract

Background: Studies have reported that food-related attention bias (AB) may perpetuate maladaptive eating behaviour. However, the mechanisms that underlie food-related AB remain unclear. Recent meta-analyses have shown that appetitive motivational state factors, e.g., craving and hunger, are associated with food-related AB. As such, it is of clinical interest that we clarify the role of AB towards food in populations characterised by high levels of craving for food and self-reported hunger, including those with binge eating disorder (BED). Accordingly, the present study evaluated AB for high- and low-calorie food stimuli in adults with obesity (body mass index [BMI] $\geq 30 kg/m^2$) with and without a diagnosis of BED.

Method: Twenty adults with obesity with BED and twenty controls with obesity (but not BED) completed a visual probe task with high- and low-calorie food stimuli paired with non-food stimuli. AB was assessed indirectly by computing an AB score derived from reaction times (RT; score = $RT_{\text{Incongruent Trials}} - RT_{\text{congruent Trials}}$), where higher scores indicated greater bias towards food. Eye-tracking was used to directly assess attention for food-related stimuli (dwell bias), where higher scores indicated greater AB toward food.

Results: AB towards food did not significantly differ between groups, regardless of whether AB was assessed directly or indirectly. Participants in both groups showed AB toward high-calorie food, regardless of whether AB was measured directly or indirectly. Of note, however, in both instances, mean AB indices were descriptively higher in the BED group. Only participants with BED showed an AB toward low-calorie food stimuli, and this was only seen when AB was assessed by eye-tracking. In both groups, AB toward high-calorie food was positively correlated with current food craving, however, AB toward low-calorie food was positively correlated with current craving in the BED group only.

Conclusion: Although we observed no significant differences between the two groups, there was a trend towards AB being elevated the group with BED, an AB towards low-calorie food cues was only observed in BED. Moreover, significant positive correlations between craving for food and food-related AB suggest food-related AB may be particularly relevant in BED.

3.1 Introduction

As outlined in Chapter 2, attention bias (AB) towards emotional stimuli may contribute to the development and maintenance of psychiatric disorders, most prominently mood and anxiety disorders. As a result, there is interest in developing interventions that might directly alter emotional AB. However, AB does not occur exclusively in the context of emotion, and studies have shown that AB towards other salient stimuli may perpetuate maladaptive behaviours. Indeed, food-related AB has been implicated in the maintenance of eating and weight disorders, including binge eating disorder (BED) and obesity (Appelhans et al., 2016; Brooks et al., 2011; Nijs & Franken, 2012; Stojek et al., 2018).

As with emotion, food-related ABs are commonly assessed using the emotional Stroop task (with food words), the visual probe task (or dot probe task), and the visual search task (see Hardman et al., 2021 for a detailed overview of methodologies and stimuli). Using these paradigms, AB for food can be assessed indirectly by measuring response latencies to food cues versus control cues during the task. However, measures of AB derived from response latencies have poor reliability (Ataya et al., 2012; van Ens et al., 2019; Waechter et al., 2014). More reliable measures of AB may be obtained by directly monitoring participants' eye movements as they complete the task (i.e., eye-tracking; Christiansen, et al., 2015; van Ens et al., 2019). Using eye-tracking, facilitated attention engagement (i.e., the speed with which attention is drawn towards a salient stimulus, such as food, relative to a non-salient stimulus) can be measured either through saccade latency (i.e., the time between target presentation and initial gaze shift) or initial orientation bias (i.e., the proportion of trials for which the initial gaze was oriented towards salient stimuli versus neutral stimuli). Similarly, difficulties with attention disengagement (i.e., the degree to which a salient stimulus captures attention and impairs the shifting of attention away from that stimulus) may be inferred by the difference in total dwell time on salient stimuli, as opposed to neutral stimuli, known as overall gaze duration bias.

Studies investigating AB as a potential maintenance mechanism in individuals with overweight and obesity reported mixed findings. For example, a systematic review concluded that individuals with obesity and overweight show greater AB to food cues compared to those with healthy weight (Hendrikse et al., 2015). However,

findings from recent meta-analyses suggest that this may not be the case (Hagan et al., 2020; Hardman et al., 2021). In their meta-analysis of 19 studies examining AB to food in participants with overweight and obesity relative to healthy weight controls, Hagan et al. (2020) found no significant difference between groups regardless of the task used to measure AB or the component of AB assessed (e.g., automatic attention allocation/facilitation bias or sustained attention or duration bias). Similarly, in their meta-analysis of 90 studies of AB towards food in healthy populations across the weight spectrum, Hardman et al. (2021) found no evidence to suggest that body mass index (BMI) was positively associated with food-related AB. Instead, Hardman et al. (2021) reported that craving, hunger, and food consumption were significantly associated with elevated AB towards food.

Consistent with this finding, altered AB towards food has been described in BED, i.e., a psychological disorder characterised by craving for food, elevated self-reported hunger, and loss-of-control over eating behaviour. For example, in a small study which administered a modified Stroop task during functional magnetic resonance imaging (fMRI) in a sample with bulimia nervosa (BN, n = 13), BED (n = 12), and healthy controls (n =14), it was reported that task accuracy was diminished in participants with BN and BED, relative to healthy controls (although this difference was only significant in BN) (Lee et al., 2017). Moreover, BOLD response to food stimuli (derived by contrasting food stimuli blocks with neutral stimuli blocks) was stronger in regions linked to reward processing (e.g., ventral striatum) in participants with BED than in healthy controls (Lee et al., 2017). These data suggest that AB towards food in BED may be related to elevated reward sensitivity and strong "bottom-up" responses that impinge on top-down attention control. Indeed, this hypothesis is supported by findings from other trials in BED that have indirectly assessed AB towards food using behavioural paradigms (Deluchi et al., 2017; Lyu et al., 2017; Schmitz et al., 2014).

Where AB has been assessed directly (e.g., using eye-tracking), findings are mixed. For example, one study using a free exploration paradigm and a modified anti-saccade task found that, compared to weight-matched (n = 25) and healthy weight (n = 25) controls, women with overweight or obesity and BED (n = 25) showed an attention maintenance bias towards high- and low-calorie food compared to non-food stimuli, compared to women with obesity and women with normal weight (Schag et

al., 2013). Similarly, an eye tracking study in adults with healthy weight with and without binge eating (*n = 27* and *n* = 30, respectively) found that adults who binge eat attended to high- and low-calorie food items for significantly longer, and significantly earlier, than non-binging controls, when viewing in real-world scenes (Popien et al., 2015). In contrast, Sperling et al. (2017) found no evidence for an initial orientation bias towards food in their study of adults with full- and sub-syndrome BED (*n* = 23) and matched-controls (*n* =23). However, initial attention towards food and longer sustained attention for food were both positively correlated with greater BED severity.

These findings may be explained by a motivational conflict or ambivalence towards food. Specifically, it has been theorised that obesity, and perhaps BED, may be characterised by an attraction to food-related stimuli during the initial orienting stage of attention processing, and avoidance of food-related stimuli or a reduction in bias towards them when attention must be maintained (Jansen et al., 2015; Nijs & Franken, 2012; Nijs et al., 2010; Werthmann et al., 2011). Indeed, this hypothesis was supported by findings from a study that assessed AB at different stages of information processing in BED (Deluchi et al., 2017). Here, the authors observed that participants with BED showed an initial bias towards food, as demonstrated by faster reaction times than controls with obesity when stimulus presentation was brief (200ms), and that participants with BED experienced difficulties disengaging with food stimuli, as demonstrated by faster reaction times than controls with obesity when stimulus presentation was slightly longer (500ms). However, when stimuli were presented for durations which required the maintenance of attention (2000ms), bias scores approached zero in both groups, suggesting subsequent avoidance of food stimuli (Deluchi et al., 2017). In BED, this pattern of approach-avoidance may contribute to craving and negative-affect, which is an established trigger for loss of control eating behaviour (e.g., Leehr et al., 2015).

Overall, findings in both obesity and BED highlight that the relationship between AB towards food and overeating behaviour is complex and may be accounted for by factors beyond BMI. More specifically, recent studies highlight the role of appetitive motivational states (Hardman et al., 2021) and altered cognitive control and reward related neural processing (Lee et al., 2017). As such, there is a clear need to further our understanding of AB towards food in populations characterised by high levels of

craving for food and self-reported hunger, such as BED. Clarifying the extent to which AB towards food may distinguish BED from obesity may provide useful insight into BED aetiology and open the door to new avenues for treatment.

Few studies have directly measured AB towards food in BED. Indeed, to the best of our knowledge, no study has previously assessed AB towards food using eye-tracking during the visual probe task in adults with BED. This may be explained by limited access to the tools needed to directly assess AB (e.g., eye-tracking equipment), and the high cost associated with their acquisition. Although unlikely to rival the precision of lab-based technologies, consideration for novel, scalable and affordable webcam-based eye-tracking solutions are warranted. As such, the present study aimed to evaluate AB for high- and low-calorie food stimuli in adults with obesity with BED and adults with obesity without BED using both direct (webcam-based eye-tracking) and indirect (reaction time) assessment methods during the visual probe task. Given recent meta-analytic findings, and those reported in previous studies of BED, we hypothesised AB towards food to be elevated in participants with BED relative to those without BED. Additionally, given that appetitive motivation and craving may elevate AB towards food, we hypothesised that AB towards food would be more pronounced for high-calorie foods, than low-calorie foods, in both groups.

3.2 Study aims and hypotheses

This cross-sectional study aimed to measure AB toward high- and low-calorie food stimuli in adults with obesity and without BED and evaluated whether patterns of AB differ between groups.

Hypotheses:

1. Participants were fasted, so we expected both groups (i.e., obesity with and without BED) to show AB towards high-calorie food and we hypothesised that AB would be significantly and positively correlated with appetitive motivation factors (i.e., hunger and craving).
2. Given that appetitive motivation factors, particularly craving, have been associated with AB towards food, we hypothesised that AB towards high-calorie foods would be more pronounced in obesity with BED than obesity without BED.
3. As previous studies have reported AB towards high-calorie but not low-calorie foods in participants with obesity with and without BED, we do not expect participants from either group to show AB towards low-calorie food stimuli.

3.3 Methods

3.3.1 Participants

Twenty participants with obesity and BED and 20 controls with obesity (but not BED) (henceforth OB controls) were recruited from the community (via advertisements on social media, research participant recruitment websites, and university-managed webpages) and from outpatient eating disorder (ED) services (participants with BED only). Participant characteristics by group are summarised in Table 1. All participants were right handed adults (aged 18 to 65) with normal or corrected-to-normal vision and a BMI $\geq 30 kg/m^2$. All participants were also required to have access to a laptop or desktop computer with a webcam which they could use when taking part. Participants were ineligible if they were vegan or vegetarian, had insufficient knowledge of the English language, reported current pregnancy or suspected pregnancy, or if they reported a history of substance use disorder, psychosis, bipolar disorder, development or neurological disorder, or borderline personality disorder. Use of psychotropic medication, other than a stable dose of an antidepressant, also precluded participation. In addition, OB controls were ineligible to take part if they reported any current or past ED, whereas participants with BED were required to meet criteria for full-syndrome BED diagnosis according to the Diagnostic and Statistical Manual for Mental Disorders - 5th Edition (American, Psychiatric Association, 2013). Presence/absence of current ED symptoms was confirmed at screening using the Eating Disorder Diagnostic Screen (EDDS; Stice, Telch & Rizvi, 2000). Participants with BED included in this study were also part of a larger randomised controlled trial (see Chapters 4, 5 and 6) and, as such, they were also required to meet additional inclusion criteria for safety reasons (see Chapter 4). Participants with BED completed measures reported here as part of their baseline (i.e., pre-treatment) assessment.

3.3.2 Ethics

All study procedures were approved by the King's College London Research Ethics Committee on the 2nd of November 2020 (Reference: LRS-19/20-20873). Approval for the related randomised controlled trial from which participants with BED were drawn was given favourable opinion by the London and Fulham NHS research ethics committee (REC Reference 20/LO/0936) on the 6th of August 2020, and approval to

begin the trial was granted by the Health Research Authority on the same day.

3.3.3 Measures

3.3.3.1 Questionnaire Measures

ED symptoms were assessed using the Eating Disorders Examination Questionnaire (EDE-Q; Fairburn & Beglin, 2008). Episodes of objective binge eating (OBE) were taken from the EDE-Q item about binge eating in the previous 28 days and self-reported weight and height were used to calculate BMI. To ensure participants were able to recognise episodes of objective binge eating, prior to completing the EDE-Q, participants were shown fictional examples of *objective* and *subjective* episodes of binge eating (See Appendix H.3).

General psychopathology was assessed using the Depression, Anxiety and Stress Scale (21 item version, DASS-21; Lovibond & Lovibond, 1996). Higher scores on the DASS-21 and its subscales indicated higher levels of psychopathology. Both instruments have strong psychometric properties and have been widely used in studies involving both clinical and community adult samples (Antony et al., 1998; Carey et al., 2019).

As in Werthmann et al. (2011), craving was assessed by asking "How strong is your craving for food right now" on a 10-point visual analogue scale (VAS), ranging from "no craving at all" (0) to "extremely strong craving" (10). Hunger and satiety were also assessed by two 10-point VAS where 0, indicated an absolute absence of hunger/satiety, to 10, indicating an overwhelming presence of hunger/satiety.

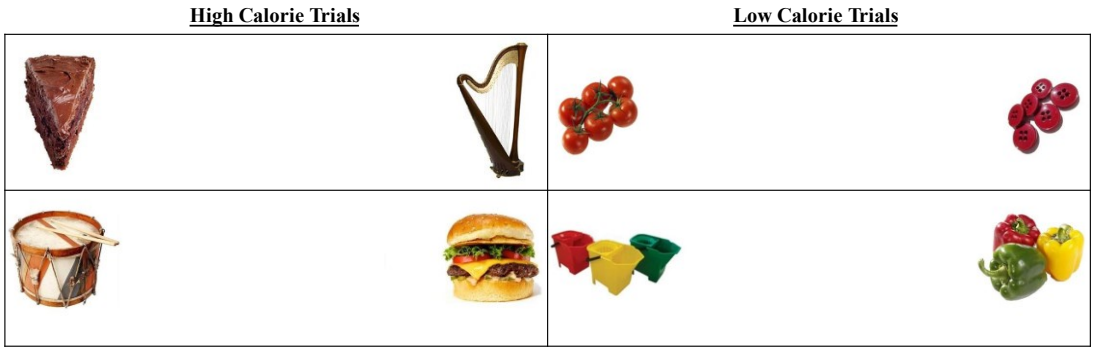
3.3.3.2 Visual probe task (VP)

The VP task (MacLeod et al., 1986) was used to assess visuo-spatial AB for food cues. Each trial began with a fixation cross presented for 100ms. This was followed by image pairs (one food image and one non-food image) that were presented simultaneously on both sides of a computer screen (3000ms). Immediately after the pictures disappeared, a probe appeared in the location of one of the stimuli (i.e., on the left or right side of the screen). Participants were instructed to press the left or right arrow key according to the location of the probe. The task consisted of two blocks of 60 trials (120 trials total). One block paired non-food pictures with high-calorie food pictures, whereas the other block paired non-food pictures with low-

calorie food pictures. The order of the blocks was randomised between participants, and image presentation was randomised within each block. The position of the food, as opposed to non-food, picture on the screen was counterbalanced within blocks to ensure food and non-food images appeared equally often on the left and right sides of the screen. Similarly, the position of the probe was counterbalanced within blocks.

Stimuli were ten high-calorie and ten low-calorie food pictures that were visually matched with one category of non-food pictures each (musical instruments or household objects, respectively) on the basis of brightness, lighting, and visual complexity (see Figure 3.1 for an example of picture pairs). High-calorie food stimuli depicted sweet (50%) and savoury (50%) foods, whereas low-calorie food stimuli depicted fruit (50%) and vegetables/salad (50%). Each set of picture pairs was presented four times (80 critical trials total). Filler trials were included using ten sets of picture pairs involving two non-food stimuli, and these were presented four times during the task (40 filler trials total). See Appendix H to review stimuli. Half of the filler trials were presented during the first block only and the other half during the second block only. Participants also completed a practice block which presented ten additional picture pairs that were not presented at any other time during the task.

Figure 3.1. Sample stimuli from the visual probe task showing high-calorie and low-calorie picture pairs.



Reaction times (RTs) were recorded as an indirect measure of AB and used to calculate behavioural AB scores. Behavioural AB scores were calculated separately for each participant by subtracting mean RT for responses to valid trials in which the probe was concealed by a food-related image (congruent trial) from those in which the target was concealed by a neutral image (incongruent trial). Mean AB score for food, as well as the mean AB score for high- and low-calorie trial types, was

calculated for each participant.

Eye movements were recorded using the participant's webcam to directly measure visual attention towards food and non-food stimuli. Prior to commencing the task, a 9-point calibration with subsequent validation procedure was conducted. This calibration was repeated after the practice trials and after each block (60 trials). The screen was divided into three areas of interest (left, right and middle) and data were analysed only for those areas displaying a stimulus (i.e., the left and right sides of the screen). Output provided estimates of total gaze time at each location for each trial, (ms and % of trial time). Dwell bias (also known as duration bias) is an established index of sustained attention allocation (Field, Mogg & Bradley, 2004; Werthmann et al., 2015). Dwell bias was calculated by subtracting the total time spent attending to the non-food stimulus (ms) from the time spent attending to the food stimulus (ms) during each trial. Mean dwell bias for food, as well as the mean dwell bias for high-calorie and low-calorie trial types, was calculated for each participant.

3.3.4 Procedure

Participant eligibility was assessed over the phone using a study-specific screening questionnaire (See Appendix G). Individuals that met inclusion criteria and chose to take part completed all study activities remotely using their personal laptop or desktop. Investigators supervised and instructed participants for the full duration of the assessment using the Microsoft Teams tool video conferencing software.

All participants were asked to fast for 4 hours prior to assessment. At the beginning of the session, the investigator greeted the participant and introduced them to the Microsoft Teams interface (i.e., ensured the participant knew how to operate their camera and microphone, knew how to return to the call if the call was dropped, and that they could locate the "chat" function). Following this, the participant completed questionnaire measures using the Qualtrics^{TM} online survey platform. Prior to launching the survey, participants were notified that the questions would ask about mood and eating behaviour, including objective binge eating. Fictional examples of objective and subjective binge eating were then presented (Appendix H.3). In addition to the EDE-Q and the DASS-21, participants also indicated whether they had fasted prior to the session as agreed (yes/no) and recorded the time at which they

last ate or drank anything other than water. While completing questionnaires, participants were invited to "mute" their microphone and switch of their webcam off, however, they were encouraged to ask questions and seek clarification as needed.

After completion of the survey, the investigator provided instructions for the visual probe task. Following this, participants were directed to complete the task using the Gorilla^{TM} online platform. This software ensures that the task occupies the full screen and suppresses notifications from other applications and webpages during task administration. After completing the visual probe task, participants performed additional tasks assessing executive function, however, these data are beyond the scope of this thesis and will be reported elsewhere.

3.3.5 Data analysis

Participant characteristics were analysed using descriptive statistics, and t-tests or chi-squared tests for group comparisons. For the visual probe task, trials were considered invalid if the response was incorrect or the RT was < 200ms or > 2000ms (Bradley et al., 2003). Eye movement data were excluded for 3 participants (BED: n=2, OB: n=1) as output indicated that calibration was lost during task administration (i.e., the participant successfully completed the 9-point calibration but moved too much during task administration, rendering eye-movement data unreliable). As such, eye movement data from the remaining 35 participants (BED: n=18, OB: n=17) were included in the data analysis. One sample t-tests were used to confirm the presence of AB (i.e., that the AB score was significantly different from zero). One way analysis of variance (ANOVA), controlling for BMI and DASS-21 total score, was used to examine between-group differences for AB overall. A mixed models ANOVA with one between-subjects factor (group: OB vs BED) and one within-subjects factor (trial type: high vs low-calorie) was used to examine whether differences in AB differed between- or within-groups as a function of trial type. Post-hoc t-tests were completed with Bonferroni correction for multiple comparisons ($p < 0.025$). The same approach was used to evaluate differences between groups of both indices of AB (i.e., behavioural AB score and dwell bias score). Independent t-tests were used to assess differences between groups for current craving, hunger and satiety ratings, and Hedge's g was used to evaluate effect size ($g \leq 0.2$ is small, $g \leq 0.5$ is medium, and ≥ 0.8 is large; Cohen, 1977). Pearson's bivariate correlations were used to assess the relationship between current hunger, craving and satiety and AB towards food.

3.4 Results

Participant characteristics are summarised in Table 3.1. Of note, participants with obesity and without BED did not differ on the basis of age, biological sex, ethnicity, or academic attainment, and we observed the expected clinical differences between the groups. Specifically, both groups were living with severe obesity and approximately 15% of participants in each sample experienced obesity-related physical health problems, whereas ED symptoms and psychopathology were elevated in BED only. Given that the DASS-21 score was significantly different between groups, subsequent analyses included DASS-21 total score as a covariate.

Table 3.1. Participant characteristics by group

	BED *(n = 20)*	**Obesity** *(n=18)*	***p*-value**
Demographic Details			
Age (mean [SD])	38.9 (8.0)	36.44 (10.3)	.445
Female sex (n [%])	18 (90.0)	16 (88.8)	.857
Ethnicity (% White)	17 (85.0)	15 (83.3)	.709
Level of education			.423
A-levels	3 (15.0)	5 (27.8)	
Undergraduate	9 (45.0)	7 (38.9)	
Postgraduate	5 (25.0)	4 (22.2)	
Other tertiary	3 (15.0)	2 (11.1)	
Clinical Characteristics			
BMI (mean [SD])	38.6 (7.3)	37.6 (4.3)	.501
EDE-Q global (mean [SD])	4.21 (0.8)	2.7 (1.2)	<0.001
EDE-Q monthly OBEs (median [SD])	20 (9.7)	0	<0.001
DASS-21 total (mean [SD])	48.3 (25.4)	14.0 (8.7)	<0.001
Antidepressant medication	9 (45.0)	1 (5.5)	<0.05
Lifetime Comorbidities			
Depression (n [%])	11 (55.0)	3 (16.6)	<0.001
Anxiety (n [%])	8 (40.0)	2 (11.1)	<0.05
Diabetes mellitus (Type II) (n [%])	5 (25.0)	4 (22.2)	.573
Prediabetes (n [%])	1 (5.0)	2 (11.1)	.459
Hypertension (n [%])	4 (20.0)	3 (16.6)	.563
Hyperlipidaemia (n [%])	3 (15.0)	3 (16.6)	.616
Hypothyroidism (n [%])	3 (15.0)	2 (11.1)	.552

P-value corresponds to t-tests or chi-squared tests for between group differences. BMI, body mass index; EDE-Q, Eating Disorders Examination Questionnaire; DASS-21, depression anxiety stress scale (21-item version); OBEs; objective binge eating episodes.

3.4.1 Craving, hunger, and satiety

Self-reported craving did not differ between groups (BED: mean = 7.62, SD = 1.14, OB: Mean = 6.24, SD = 1.92, p = .268, Hedge's g = .244), and there were no significant differences between groups for hunger (BED: mean = 5.34, SD = 3.24, OB: Mean = 5.51, SD = 3.20, p = .114, Hedge's g = .052) or satiety ratings (BED: mean = 4.44, SD = 2.86, OB: Mean = 4.12, SD = 3.32, p = .197, Hedge's g = .220).

3.4.2 Behavioural outcomes (RTs)

Table 3.2 shows the means and standard deviations for RTs for congruent and incongruent trials by group, as well as the resulting AB scores.

One sample t-tests confirmed the presence of an AB towards food stimuli, as opposed to neutral stimuli, in BED (t(19) = 3.449, p < .005) but not OB (p = .224). When limiting the analysis to trials involving high-calorie food images, a significant AB towards food emerged in OB (t(17) = 3.015, p < .01) and was retained in BED (t(19) = 1.945, p < .05). AB scores for low-calorie trials were not significantly different from zero in the BED (p = .277) or OB (p = .857) group.

One way ANOVA revealed no significant difference between-groups for overall AB score (F = 1.277, p = .266). Similarly, mixed methods ANOVA controlling for BMI and DASS-21 total score revealed no significant differences within groups (i.e., differences according to high- or low-calorie trial type; F = 1.194, p = 0.283) or between-groups (F = 0.012, p = .913) for AB score, and there was no significant group by trial type interaction (F = 0.210 = .650) (Figure 3.2).

Pearson's correlations revealed that there was a significant positive correlation between craving and AB towards high-calorie food stimuli in both groups (BED: r(20) = .562, p <.005; OB: r(17) = .485, p < .05). Tests for regression slope equality were non-significant (F = .356, p = .555) indicating that the relationship between current craving for food and attention bias score for high calorie food stimuli was equivocal when controlling for sample variability. There was no significant correlation between craving and AB for low-calorie food stimuli in BED (p = .198) or OB (p =.350). Similarly, correlations between hunger and satiety ratings, and AB towards high- and low-calorie foods were all non-significant at the p = .05 level.

Figure 3.2. Attention bias scores (mean and standard deviation) for high- and low-calorie food trials

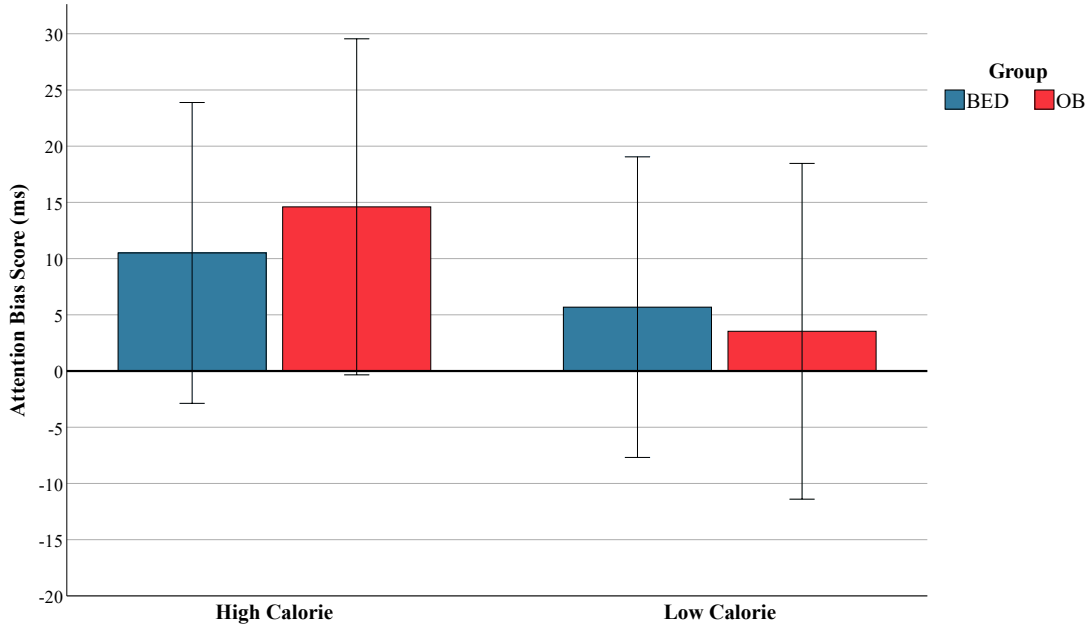


Figure Legend: Means controlling for BMI and Total Score on the DASS-21. Error Bars = 95% Confidence Interval

Figure 3.3. Scatter plot summary of attention bias score for high-calorie food trials by ratings for current craving in BED.

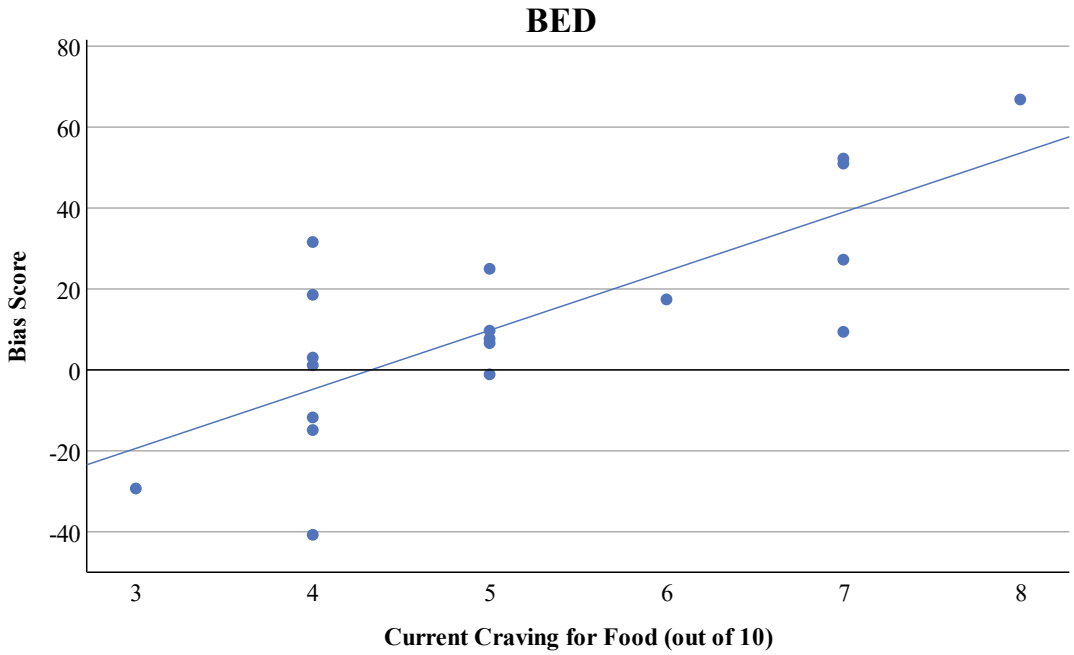
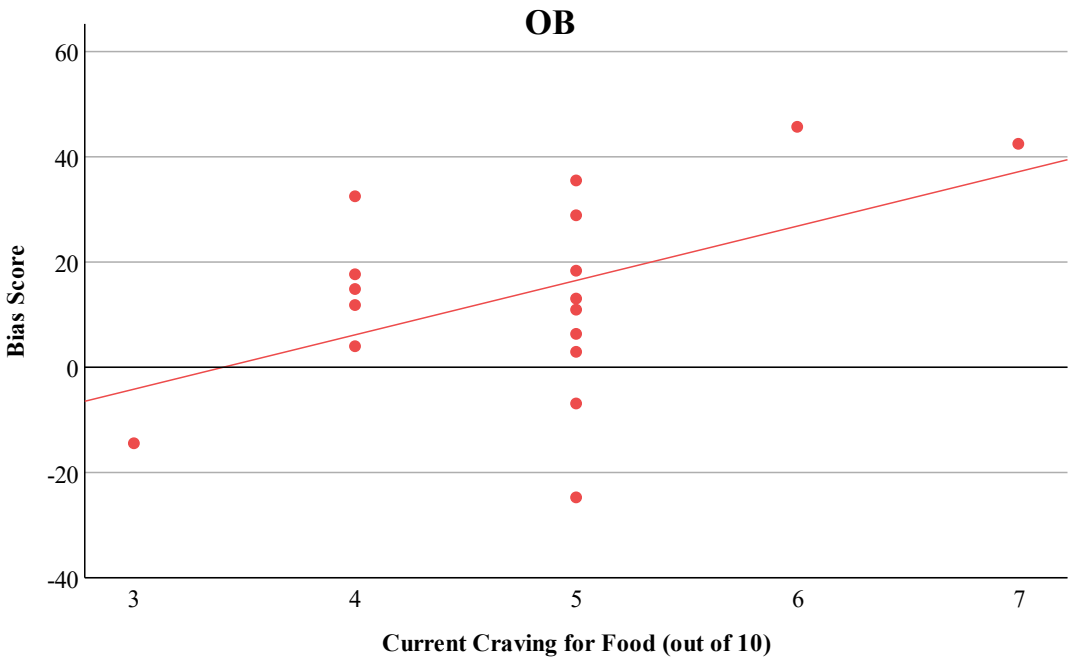


Figure 3.4. Scatter plot summary of attention bias score for high-calorie food trials by ratings for current craving in OB.



3.4.3 Eye-tracking Outcomes

Table 3.2 shows the means and standard deviations for total fixation time towards food and non-food items by group, as well as the resulting dwell bias scores.

One sample t-tests confirmed the presence of a dwell bias towards food items, as opposed to neutral items, in BED ($t(17) = 6.010$, $p < .001$) and OB ($t(16) = 2.291$, $p < .05$). Similarly, when distinguishing between high- and low-calorie trials, one sample t-tests revealed a significant bias towards high-calorie food stimuli in both groups (BED: $t(17) = 6.675$, $p < .001$; OB: $t(16) = 2.695$, $p < .01$). During low-calorie trials, only participants with BED showed a significant bias towards food items, as opposed to neutral items ($t(17) = 2.923$, $p < .005$).

One way ANOVA revealed no significant difference between-groups for overall dwell bias score ($F = 3.059$, $p = .089$). Mixed methods ANOVA, controlling for BMI and DASS-21 total score, revealed no significant within group (i.e., differences according to high- or low-calorie trial type; $F = .070$ $p = .793$) or between group ($F = 2.673$, $p = .112$) differences, and there was no significant group by trial type interaction ($F = .850$, $p = .364$) (Figure 3.5).

Figure 3.5. Dwell bias score (mean and standard deviation) for high- and low-calorie food trials

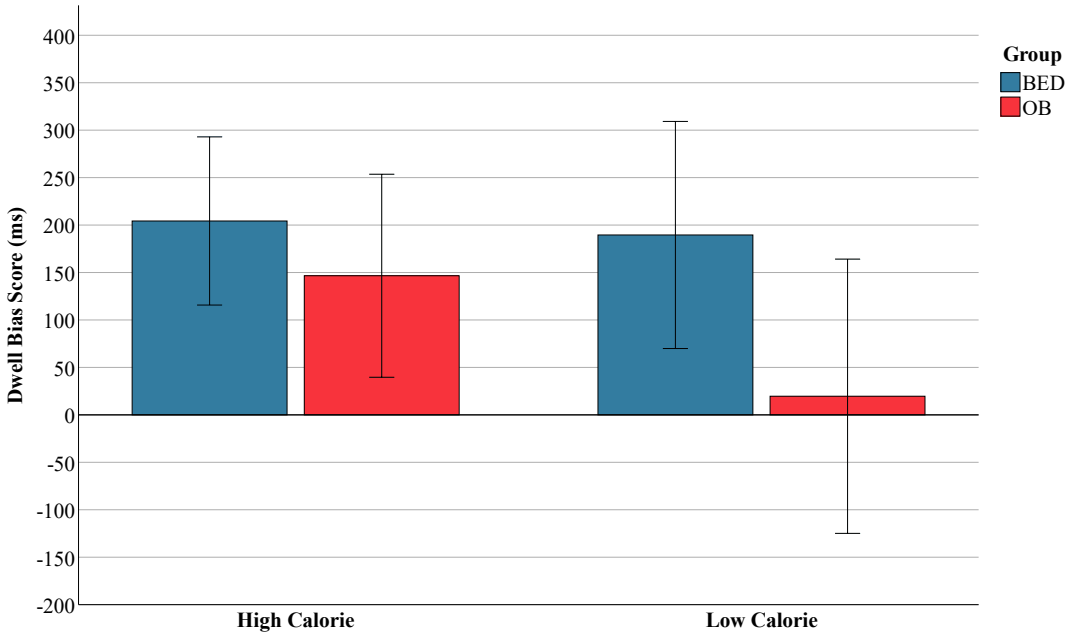


Figure Legend: Mean scores controling for BMI and DASS-21 Total Score. Error Bars show 95% Confidence Interval.

Pearson's correlations revealed that there was a significant positive correlation between craving and dwell bias towards high-calorie food stimuli in both groups (BED: $r(18) = .551$, $p < .005$; OB: $r(17) = .485$, $p < .05$). Tests for regression slope equality were non-significant ($F = .547$, $p = .465$) indicating that the relationship between current craving for food and dwell bias score for high calorie food stimuli was equal when controlling for sample variability. There were no other significant correlations between current hunger and dwell bias score, and there were no significant correlations between current satiety ratings and dwell bias towards food stimuli for OB or BED groups.

Figure 3.6. Scatter plot summary of dwell bias score for high-calorie food trials by ratings for current craving in BED.

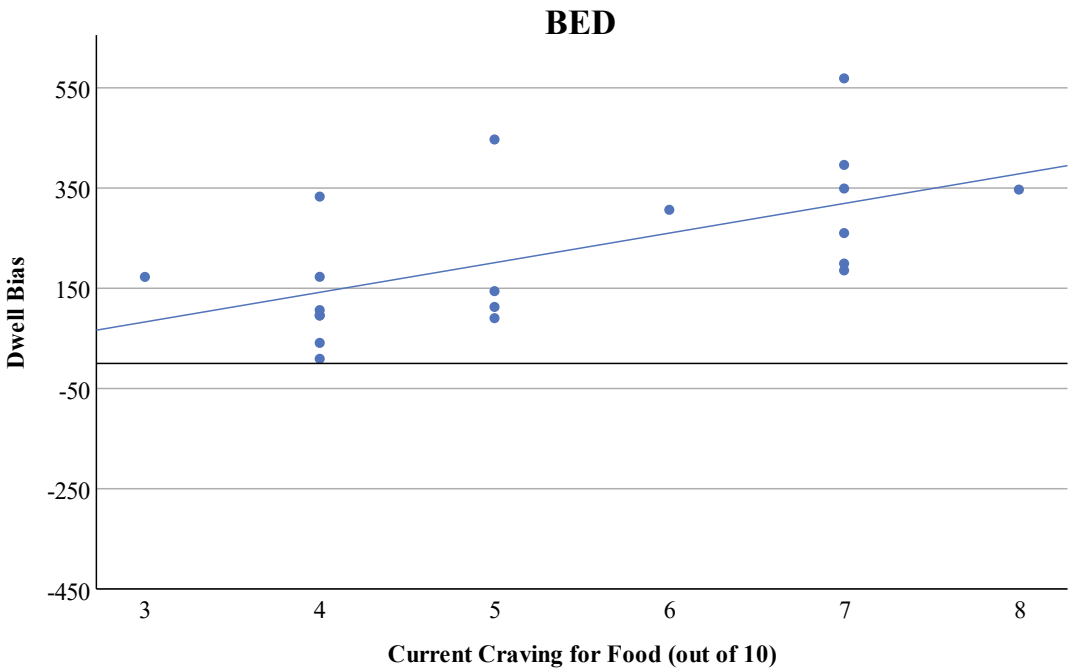


Figure 3.7. Scatter plot summary of dwell bias score for high-calorie food trials by ratings for current craving in OB.

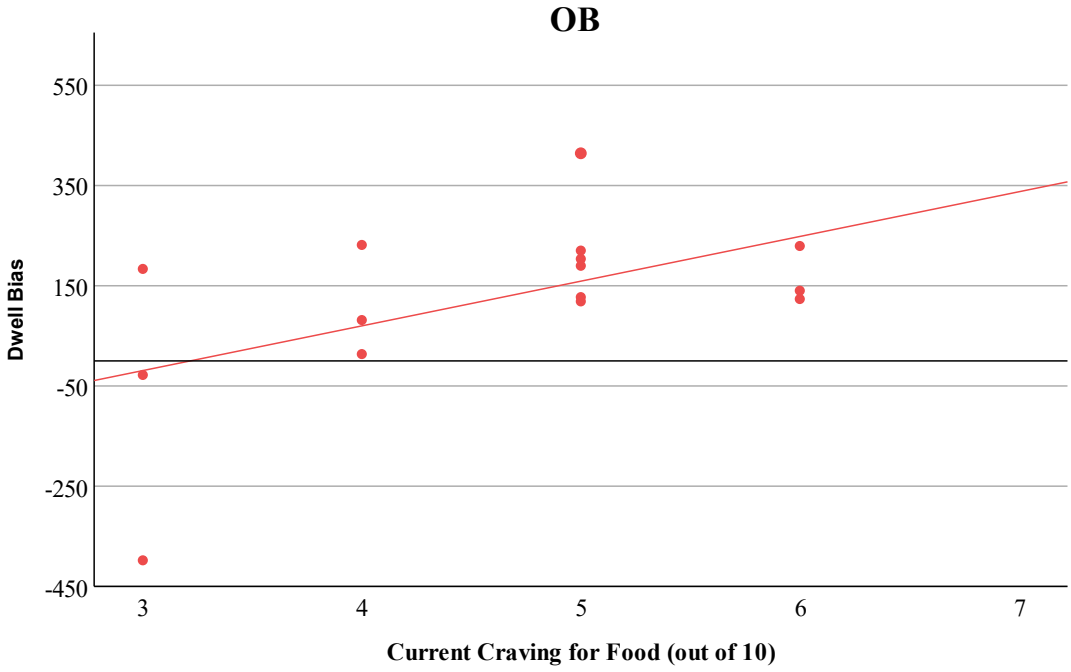


Table 3.2. Means and standard deviations for behavioural and eye-tracking indices of AB towards food (ms)

	BED *(n = 20)*	Obesity *(n=18)*	*p*-value
Reaction times			
Congruent trials	516.67 (100.74)	436.41 (63.72)	<0.05
HC trials	511.67 (102.87)	433.22 (63.49)	<0.05
LC trials	518.65 (101.78)	439.55 (66.18)	<0.05
Incongruent trials	529.88 (97.96)	442.80 (71.57)	<0.01
HC trials	529.29 (93.47)	445.94 (69.61)	<0.01
LC Trials	528.35 (106.91)	439.70 (76.63)	<0.05
AB score (overall)	13.22 (17.49)	6.39 (16.34)	.256
AB score (HC)	17.63 (22.61)	12.71 (19.02)	.506
AB score (LC)	9.69 (23.16)	0.15 (16.97)	.189
Eye Movements			
Total fixation time (neutral)	1386.47 (106.41)	1489.67 (95.77)	.537
Total fixation time (food)	1492.76 (113.03)	1512.53 (87.24)	.561
Total fixation time (HC)	1485.97 (124.00)	1519.72 (284.29)	.634
Total fixation time (LC)	1461.37 (144.82)	1464.16 (183.18)	.959
Dwell bias score (overall)	187.63 (139.61)	97.19 (174.94)	.089
Dwell bias score (HC)	221.68 (148.54)	123.41 (177.33)	.084
Dwell bias score (LC)	161.22 (246.62)	57.43 (173.33)	.174

p-value reflects outcome from one-way ANOVA. Abbreviations: AB, attention bias, *BED, binge eating disorder; OB, obesity; HC, high-calorie; LC, low-calorie; ms, milliseconds*

Table 3.3. Pearson's correlations between attention bias and self-reported craving for food, hunger and satiety by group.

		BED			OB		
		Craving	Hunger	Satiety	Craving	Hunger	Satiety
AB for Low Calorie	*r*	.368	-.134	-.065	.242	-.054	.209
	p	.110	.572	.785	.350	.836	.437
AB for High Calorie	*r*	**.562**	-.265	.149	**.485**	-.177	-.166
	p	**<.01**	.272	.544	**< .05**	.496	.539
Dwell Bias for Low Calorie	*r*	.163	.293	.141	.128	-.078	-.143
	p	.492	.210	.533	.624	.765	.598
Dwell Bias for High Calorie	*r*	**.458**	.293	.039	**.531**	.075	.431
	p	**< .05**	.210	.971	**< .05**	.791	.124

R values indicate Pearson's correlation co-efficient. Correlations at p < .05 are marked in bold.

3.5 Discussion

The aim of this study was to examine whether AB towards food stimuli distinguished adults with obesity with BED from adults with obesity without BED, and to assess whether AB towards food stimuli was related to appetitive motivation factors, including current craving for food, hunger, and satiety. Consistent with our hypotheses, both groups showed an AB towards high-calorie food stimuli, irrespective of whether AB was measured indirectly using RTs or directly using eye-tracking. An unexpected finding was that participants with BED also showed significant AB towards low-calorie food when AB was measured directly (i.e., dwell bias). This finding might suggest that the motivational salience of food, as opposed to non-food, stimuli is high in BED, even when calorie content is low.

Craving for food, but not hunger, was significantly and positively correlated with AB towards high-calorie food in both groups, which partially supported our hypothesis. Additionally, a positive correlation between craving for food and AB towards low-calorie food items was observed in participants with BED only. This finding is consistent with theoretical accounts of food-related AB derived from incentive sensitisation theory (Robinson & Berridge, 1993, 2008). Specifically, that AB is indicative of underlying appetitive motivational processes and that AB towards food is amplified when food is relevant to an individual's current motivational state.

Contrary to our hypothesis, we found no significant differences in AB towards high or low-calorie food items between groups, regardless of whether AB was assessed directly or indirectly. However, it is it is important to note that mean dwell bias scores suggested a pattern of elevated food-related AB in BED, relative to controls, which may have been become significant in a larger sample size, although this requires future research. Nevertheless, our finding that AB towards high-calorie food stimuli did not differ between groups and was not consistent with our hypothesis or findings from previous studies (Stojek et al., 2018). Differences between the present findings and those reported previously may be explained by the different methodologies used and the different stages of attention processing assessed. For example, previous studies reporting significantly greater dwell bias in BED, have assessed AB using free-viewing paradigms (Popien et al., 2015; Schmidt et al., 2016; Svaldi et al., 2015) as opposed to the visual probe task. Similarly, where AB is indirectly assessed, studies have found AB towards food in BED, relative to controls,

during the early stages of attention processing, as demonstrated by detection bias during the visual search task (Schmidt et al., 2016) or initial orientation bias using the spatial cueing task (Lyu et al., 2017; Schmitz et al., 2014). In the present trial, all stimuli were presented for 3000ms, so behavioural data relate exclusively to late-stage attention processing.

Interestingly, reaction times for all trials, regardless of stimulus type (i.e., high- or low-calorie food stimuli) were slower in the BED group than in the OB group, suggesting slower psychomotor performance in the BED group. Poor psychomotor performance has been previously associated with overweight and obesity. A recent study of psychomotor functioning in women with BED and normal weight (n = 23) or overweight (n = 32), and healthy controls with normal weight (n = 29) or overweight (n = 48), reported that psychomotor performance deteriorated as a function of BMI, with higher BMI associated with poorer performance, regardless of BED (Eneva et al., 2017). Psychomotor performance is the coordination of a cognitive activity and motor performance, and it is thought to be affected by disturbances to executive functioning. Altered executive functioning has been reported in both BED and obesity, and the extent to which difficulties may be exacerbated by BED remains unclear. In the present study, self-reported BMI did not differ between groups, however, it is possible that weight and height were underestimated and that there were differences between groups that were not accounted for. Indeed, studies have shown that adults tend to under-report their own weight, and that the gap between self-reported weight and actual weight increases with obesity (Olfert et al., 2018). Future studies should consider more objective options for assessing overweight and obesity, including in-the-lab assessment of height and weight, use of body-composition metrics, or other anthropometric assessment tools (e.g., waist circumference).

The absence of between-group differences may also be related to appetitive motivation as participants in the present study were fasted and therefore expected to be experiencing craving and hunger. Given that BED has been characterised by reduced satiety sensitivity and high levels of craving for food (Boutelle et al., 2017; Giel, Bulik, et al., 2022), future studies in unfasted samples may prove more effective for delineating differences in AB towards food in obesity with and without BED.

In the present study, the between-group effect size for dwell bias for high calorie food stimuli was F = .273, which is considered to be moderate (Cohen, 1988). With a significance criterion of α = .05 and power = .80, the minimum sample size needed to detect a difference between groups with this effect size is N = 108 (54 participants per group). Thus, the present findings should be viewed as preliminary, and consideration should be given to methodological limitations when designing subsequent studies of attention bias in BED and OB.

Several limitations of the present study should also be considered. First, when response latencies are used to examine AB during the dot probe task, the duration of stimulus presentation is usually varied so that different stages of attention processing may be assessed. For example, past research has suggested that cues presented for ≤200 ms may be used to assess automatic orientation of attention, that cues presented for ~500ms may be used to assess attention disengagement, and that cues presented for ≥500 ms may be used to assess maintained attention (Field & Cox, 2008). In the present trial, all stimuli were presented for 3000ms, so behavioural data relate exclusively to late stage attention processing. It is also noteworthy that AB indices based on response latencies during the dot-probe task have been shown to have poor internal reliability and test-retest reliability (see Bar-Haim et al., 2007 for review), so continued use of these indices is discouraged.

Second, although eye-tracking methods may offer more reliable assessment of AB and provide greater insight into the components of biased attention (Waechter et al., 2014), current webcam-based technologies may not be well-suited to the assessment of AB. Webcam-based eye-tracking is scalable, portable, and cost-effective, making it an appealing alternative to stationary, laborious, and expensive lab-based methods. However, at present, studies suggest that webcam-based technologies may not be able to accurately detect gaze patterns (e.g., fixations and saccades), thereby limiting their utility when directly assessing AB. For example, pilot studies using the Gorilla^{TM} webcam-based eye-tracking program have reported that fixations, saccades, and blinks could only be accurately detected in ~30% of participants, whereas more basic approaches (e.g., region of interest analysis) produced accuracy comparable to lab-based assessment (Anwyl-Irvine et al., 2020). Indeed, in the present study, only region of interest analyses could be conducted, so only one component of AB (dwell bias) could be directly assessed. However, webcam-based

eye-tracking tools are becoming more numerous, and some studies using different software have suggested that web-based eye-tracking may produce data of comparable quality to lab-based equipment for "simple" eye-tracking paradigms. For example, Semmelmann and Weigelt (2018) measured viewing patterns during three paradigms (a fixation task, a pursuit task, and a free-viewing task) in the lab and online (i.e., using webcam-based eye-tracking). Here, the authors reported that the accuracy of gaze pattern detection using webcam-based eye-tracking was comparable to that achieve using lab-based equipment (offset of ~191 pixels in the lab vs ~211 pixels using webcam). However, given low sampling rates and high levels of variability within the data, webcam-based eye-tracking may not be ready for applications that require detailed spatial resolution of fixations or high spatio-temporal resolution, including visual attention paradigms. As a result, studies prioritise the use of lab-based eye-tracking equipment when directly assessing AB.

Third, recent studies have suggested that the visual probe task, even when paired with eye-tracking, may not be the optimal tool for assessing AB. Rather, free-viewing paradigms have received superior psychometric evaluations in both clinical (e.g., Soleymani, et al., 2020) and non-clinical populations (e.g., Veerapa et al., 2020). Moreover, when paired with eye-tracking, free-viewing paradigms may be used to assess AB across the early, middle, and late stages of attention processing, particularly when presentation duration is long (> 3000ms; Hardman et al., 2021). Thus, we recommend that future studies use of free-viewing paradigms, rather than the visual probe task.

Fourth, the food stimuli used to assess attention bias were not personalised, so participants may have varied in the extent to which they "liked" or were familiar with the food stimuli used. Additionally, participants were not excluded if they were intolerant to certain foods (e.g., foods containing lactose or gluten) and data were not collected about food intolerances. It is possible that some participants in this study had food intolerances, and that foods presented during the VP task were among those they avoid (e.g., cheese). No study has examined attention control in the context of poorly tolerated or disliked foods, nevertheless, we expect that people would respond to these stimuli in an atypical manner. Future studies must employ more stringent measures to control for this effect on attention towards food. This may involve the use of additional inclusion/exclusion criteria (i.e., excluding individuals with food

intolerances) or, preferably, the use of personalised food stimuli. Where personalisation is not feasible, participants' views about the food stimuli (e.g., the extent to which they are liked, perceived taste, perceived calorie content) should be assessed so that these confounds can be adequately controlled for.

Finally, as BED diagnosis was assessed at telephone screening and confirmed using the EDE-Q, it is unlikely that individuals in the BED group did not meet DSM-5 criteria for BED or that those in the OB group met criteria for BED at the time of assessment. Nevertheless, studies have shown that sensitivity and specificity is poorer for EDE-Q items assessing complex overeating behaviours (i.e., binge eating), so it is possible that binge eating behaviour was under-reported in this study (Reas et al., 2006). Alternative instruments, including the Eating Disorder Examination (clinical interview; Fairburn, Cooper & O'Conner, 2014) and the Binge Eating Scale (Gormally et al., 1982), have been shown to provide a more reliable and sensitive assessment of BED symptoms, and should be considered in future studies involving participants with BED.

Overall, our findings suggest that both groups present with a strong AB towards high-calorie food stimuli, and that this AB may be amplified in the context of craving. Although we did not find significant differences between groups, it is important to note that AB towards low-calorie foods was descriptively higher in participants with obesity with BED and the relationship between AB towards high-calorie food cues and craving was stronger in this group. Taken together, it is possible that AB towards food is distinct in obesity with BED, when compared to obesity without BED. Future studies using free-viewing paradigms which manipulate appetitive motivational factors will help to clarify this.

Chapter 4. Does concurrent self-administered transcranial direct current stimulation and attention bias modification training improve symptoms of binge eating disorder? Protocol for the TANDEM feasibility randomised controlled trial

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A copy of the article is provided in Appendix A. The formatting of this article has been amended here for stylistic consistency, but the body of the text remains unchanged.

Author contribution: The TANDEM study was conceptualised and designed by the candidate with her supervisors, Professor Ulrike Schmidt and Professor Iain Campbell. The candidate drafted the chapter and received constructive feedback from her supervisors, Professor Ulrike Schmidt and Professor Iain Campbell, and from peer reviewers from *Frontiers in Psychiatry*.

Abstract

Background: Binge eating disorder (BED) is a common and disabling problem associated with impaired cognitive control. Preliminary studies show that brain-directed treatments, including transcranial direct current stimulation (tDCS) and attention bias modification training (ABMT), improve cognitive control and alleviate symptoms of BED. When combined, tDCS may enhance the effects of ABMT, and vice versa, thereby improving treatment outcomes.

Methods: This protocol describes a feasibility single-blind randomised sham-controlled trial of concurrent self-administered tDCS and ABMT in adults with BED (The TANDEM Trial). Eighty adults with BED will be randomly assigned to one of four groups: ABMT with real or sham self-administered tDCS, ABMT only, or waiting list control. In the treatment arms, participants will complete 10-sessions of their allocated intervention over 2-3 weeks. Outcomes will be assessed at baseline (T0), immediately post-treatment (T1), and 6 weeks after end of treatment (T2), and at comparable timepoints for participants in the waitlist control group. Feasibility will be evaluated by assessing recruitment/retention rates and blinding success. Acceptability will be assessed quantitatively via participant ratings and qualitatively via semi-structured interviews. Episodes of binge eating at follow-up will be the primary clinical outcome and rate ratios from Poisson regression will be reported. Secondary outcomes will assess changes in ED and general psychopathology, attention bias towards high-calorie foods, and executive function.

Discussion: It is hoped that data from the trial will contribute to the development of neurobiologically informed treatments for BED, provide insights into the potential use of at-home variants of tDCS, and inform the design of future large scale trials.

4.1 Introduction

Binge eating disorder (BED) is a common and disabling eating disorder (ED) affecting 1-3% of the global population (Giel, Bulik, et al., 2022). It is characterised by recurrent episodes of binge eating accompanied by feelings of loss of control and subsequent distress. Episodes occur in the absence of compensatory behaviours intended to prevent weight gain (American Psychiatric Association, 2013). Among individuals with BED, psychiatric and physical health comorbidities are common; nearly 80% of those diagnosed with BED will suffer from another psychiatric disorder during their lifetime (Mustelin et al., 2018), and up to 88% live with overweight or obesity, increasing individual risk for obesity related physical health problems (Wassenaar et al., 2019). Consequently, the economic and quality of life burden associated with BED is substantial (Le & Mihalopoulos, 2021; Santomauro et al., 2021; Streatfeild et al., 2021).

Psychotherapy (particularly cognitive behaviour therapy (CBT)) and self-help interventions are recommended first-line treatments for BED (Giel, Bulik, et al., 2022). However, only about half of those who complete treatment report a significant reduction in, or abstinence from, binge eating in the 12-months following the end of treatment: moreover, neither treatment yields a significant or sustained reduction in weight (Hilbert, 2019). With respect to pharmacotherapy, second-generation antidepressants, anticonvulsants, and central nervous system stimulants produce short-term reductions in episodes of binge eating and are routinely used when treating BED. However, drug-driven reductions in binge eating episodes are not sustained beyond 3-6 months (Hilbert, 2019). Lisdexamphetamine, a central nervous system stimulant, is the only drug approved for use in the treatment of moderate-severe BED. However, the effect of the drug on ED psychopathology and mood remains unclear, and data on the long-term maintenance of effects are lacking. There are also significant risks associated with the drug's use; little is known about the effects of long-term administration, and rates of adverse events and premature discontinuation of the drug were elevated in randomised controlled trials (RCTs) (Hilbert, 2019; Schneider et al., 2021). It is possible that combining psychotherapy with pharmacotherapy may produce superior outcomes from treatment, however, findings from a recent meta-analysis yielded minimal support for this hypothesis; of the 12 included trials, only two reported that combined treatment enhanced binge

eating and weight outcomes, both of which used anticonvulsant medications, and only two reported modest improvements in weight loss, but not binge eating, outcomes, both of which used the weight-loss medication, Orlistat (Reas & Grilo, 2021).

It is widely agreed that novel treatments informed by neurobiological models of illness are needed (Schmidt & Campbell, 2013). Current models propose that emotion dysregulation, elevated food cue reactivity, and executive dysfunction, are central to the aetiology and maintenance of BED (Blume et al., 2018; Boswell & Grilo, 2021; Cury et al., 2020; Iceta et al., 2021; Leehr et al., 2015; Smith et al., 2021). These difficulties may indicate a broad impairment in cognitive control, and therefore aberrant functioning of the brain's cognitive control network. Cognitive control is the ability to orchestrate thought and action in accordance with internal goals and relies on prefrontal brain regions (e.g., the dorsolateral prefrontal cortex [DLPFC]) and associated neural networks (Miller & Cohen, 2001). In this framework, the affective reactivity (i.e., craving and emotional reactivity) and poor self-regulatory abilities reported in BED may be a consequence of impairments in cognitive control, and interventions which improve cognitive control may facilitate remission from BED.

Neurocognitive training is one tool which may be used to improve cognitive control. One class of neurocognitive training programmes, known as cognitive bias modification (CBM) uses experimental paradigms to change biased cognitive processes which perpetuate maladaptive behaviour (Jones et al., 2016). Attention bias modification training (ABMT) is a form of CBM which aims to alter the automatic allocation of attention towards salient cues. Food-specific variants of ABMT, which were developed for use in binge-type EDs and obesity, train individuals to avoid salient high-calorie food cues and attend to neutral and low-calorie food cues (Renwick et al., 2013). Meta-analyses of RCTs in healthy volunteers have revealed that a single session of food-specific ABMT is associated with a significant short-term reduction in high-calorie food consumption (medium effect size) (Turton et al., 2016) and a significant short-term reduction in bias towards high-calorie foods (medium effect size) (Fodor et al., 2017). Though few studies have used food-specific ABMT in BED, those that have report promising outcomes from treatment. One study reported that a single session of ABMT was

associated with a significant short-term reduction in subjective food craving (Schmitz & Svaldi, 2017). Another open feasibility trial delivered eight weekly sessions of ABMT and reported significant post-treatment reductions in weight, ED symptoms, episodes of binge eating, and attention bias towards food, and these were sustained to 3-month follow-up (Boutelle et al., 2016). Thus, although data on the long-term effects of ABMT are lacking, the available evidence suggests that ABMT may improve affective regulation in the context of food (i.e., cognitive control), and may have clinical utility in BED.

Non-invasive brain stimulation (NIBS) may also be used to modify functioning of cortical regions or networks implicated in BED (Dalton et al., 2018; Dalton et al., 2017). Transcranial direct current stimulation (tDCS) is a NIBS technique which may be particularly well suited to the treatment of BED: it is a safe and well tolerated technique which is inexpensive, portable, easy to use, and suitable for remote self-administration (Brunoni et al., 2019; Moffa et al., 2018). In tDCS, a constant weak direct current is applied via electrodes placed on the scalp to increase (anodal tDCS) or decrease (cathodal tDCS) cortical excitability. Specifically, tDCS modulates network dynamics within functionally connected areas beyond the cortical regions located beneath the electrodes. As a result, tDCS has the potential to modulate task- or symptom-specific neural networks. These changes in cortical excitability outlast the stimulation period (up to 60 minutes after a single-session) and, with repeated administration, may lead to lasting changes in brain function (Brunoni et al., 2019). In light of this, tDCS is being applied to the treatment of psychiatric disorders with moderate success, particularly in major depression. However, questions remain about optimal participant/patient selection, parameters for stimulation, mechanisms of action and the effects of long-term use.

Proof-of-concept studies suggest that tDCS may be effective for the treatment of binge-type EDs. In bulimia nervosa (BN), a proof-of-concept RCT with 24-hour follow-up, indicated that a single-session of right DLPFC anodal tDCS improves ED psychopathology, reduces craving for food, reduces urge to binge, and improves self-regulatory control during reward related decision making (Kekic et al., 2017). In BED, a single-session RCT using right DLPFC anodal tDCS reported a short term reduction in craving for food and desire to binge eat in participants who received real tDCS (Burgess et al., 2016). This finding was replicated in a sham-controlled

crossover trial: following a single-session of right DLPFC anodal tDCS, short-term improvements in food-related response inhibition and craving for food were observed in participants who received real 2mA tDCS stimulation, as opposed to real-1mA or sham stimulation (Max et al., 2021).

Two studies have examined the effect of multiple sessions of tDCS on BED symptoms. A randomised sham-controlled trial involving 32 adults examined the effect of 10 sessions of tDCS on attention bias towards food, craving for food, and cognitive flexibility (Afzali et al., 2021). In this trial, tDCS was given with the anode over the left DLPFC and the cathode over the right DLPFC (2mA/20 minutes). Sessions were three/week until 10 sessions had been completed. At post-treatment and 45 day follow-up, real tDCS treatment was associated with a greater reduction in attention bias towards food, a greater reduction in craving for food, and an improvement in cognitive flexibility. However, effect sizes were small, and the authors acknowledged several study limitations, including a small sample (n=32) and concerns about the effect of poor eye-tracker calibration on the reliability of attention bias outcomes.

Our group has also recently completed an RCT of six sessions of right-anodal tDCS targeting the DLPFC delivered over three weeks in adults with BED (n=65, Gordon et al. (2019) for protocol). In this trial, we examined whether symptoms of BED were improved by an intervention involving the concurrent delivery of tDCS and approach bias modification training, a form of CBM which targets approach bias towards high-calorie foods. Participants were randomly allocated to one of three study groups (approach bias modification training with real tDCS, approach bias modification training with sham tDCS, or wait-list control) and outcomes were assessed at baseline, 3-weeks post-randomisation, and 7-weeks post randomisation. Clinical and neurocognitive outcomes are yet to be published; however, findings from a qualitative study of the treatment experience indicate that this combined approach to treatment is tolerable and acceptable (Gordon, Williamson, et al., 2021).

It has been suggested that the efficacy of tDCS may depend on the functional state of the brain at the time of stimulation. If this is true, then greater and longer-lasting neuroplastic effects might be achieved when tDCS and CBM co-activate a disorder-related neural network (Vanderhasselt & Ottaviani, 2022). This may be because, by altering the relationship between excitatory (glutamatergic) and inhibitory

(GABAergic) systems in the brain (Krause et al., 2013), tDCS creates optimal conditions for memory reconsolidation, a process which may re-enforce the new learning which takes place during CBM. Similarly, CBM promotes the activation of disorder relevant brain areas, and this might enhance the effectiveness of stimulation. Consistent with this, several studies in anxiety, depression, and substance abuse disorders have reported superior outcomes from treatment when tDCS was combined with interventions which activate cognitive control regions (Heeren et al., 2015; Heeren et al., 2017; Rigi Kooteh et al., 2019).

In summary, concurrent tDCS and food-specific CBM may be a promising treatment, or adjunct to treatment, for BED. This is because of (a) evidence suggesting that tDCS and food-specific CBM may independently produce therapeutic effects in BED, and (b) the neurobiological rationale for combining these two treatments. Moreover, with the recent arrival of tDCS devices intended for supervised self-administration, both interventions can now be safely provided in the home, thereby increasing their accessibility and scalability. Accordingly, we present the protocol for a feasibility randomised controlled trial of concurrent at-home self-administered tDCS and food-specific ABMT in BED (The TANDEM trial).

4.2 Study Aims

The primary aim of the TANDEM trial is to assess the feasibility of using 10 sessions of concurrent food-specific ABMT (henceforth, ABMT) and self-administered tDCS targeting the DLPFC (anode right/cathode left montage) as a treatment for BED. This intervention will be compared to training in combination with sham stimulation, stand-alone training, and a "no treatment" waiting control condition. In doing so, we aim to acquire key information to inform the design of a large-scale RCT.

Specifically, we aim to:

a) estimate the rate ratio for the proposed primary outcome, change in the number of monthly episodes of binge eating from baseline to follow-up. This will inform the sample size calculation for a large-scale RCT.
b) explore the feasibility of conducting a large-scale RCT of at-home self-administered concurrent tDCS and ABMT in adults with BED by assessing recruitment, attendance, and retention rates;
c) assess acceptability by examining participant ratings of treatment acceptability and tolerance, and by evaluating feedback provided during semi-structured interviews;
d) determine the best instruments for measuring primary and secondary outcomes in a full trial by examining the quality, completeness, and variability in the data.

The primary clinical endpoint will be the change in monthly episodes of binge eating from baseline to follow-up. Secondary aims will focus on evaluating changes in overall ED pathology and general psychopathology, changes in attention bias towards high-calorie foods, and changes in executive functioning from baseline to 6-weeks post-treatment completion.

4.3 Methods

Reporting of this protocol is guided by the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (Chan et al., 2013) and the Consolidated Standards of Reporting Trials (CONSORT) statement extension for feasibility randomised controlled trials (Eldridge et al., 2016). The TANDEM trial has also been registered with the U.S. National Institute for Health (NIH) Clinical Trials database (clinicaltrials.gov; trial identifier: NCT04424745). Copies of all documentation relating to research ethics are provided in Appendix C.

4.3.1 Study design

TANDEM is a randomised single-blind sham-controlled feasibility trial with four parallel arms: ABMT + real tDCS, ABMT + sham tDCS, ABMT only, and 8-week wait-list control. After baseline assessment (T0), participants will be randomly allocated to a study group. Those allocated to treatment groups will then complete 10 sessions of their allocated treatment over 2 weeks. Outcome measures will be completed first at baseline (T0), then again immediately after completing treatment or after 2-weeks waiting (T1), and finally 6-weeks after completing treatment, or after 8-weeks of waiting (T2). Process outcomes will also be assessed at each treatment session.

4.3.2 Participants

4.3.2.1 Recruitment

Recruitment for this trial began in March 2021 and ran for 12 months. Participants will be recruited from the community (via advertisements on social media, research participant recruitment websites, and university-managed webpages), and from the South London and Maudsley outpatient ED service. See Appendix F for copies of community and patient facing recruitment materials.

People interested in the study will receive verbal and written information about the study rationale, aims, and methodology. Specifically, participants are told that there is tentative evidence to suggest both tDCS and ABMT may reduce craving for food and episodes of loss of control eating, and that the present study will be the first to examine whether combining these two interventions may alleviate symptoms of BED. After providing written consent, participants will be screened against inclusion

and exclusion criteria (See Appendix G for screening instruments). Participant information and consent forms are provided at Appendix D and Appendix E.

4.3.2.2 Inclusion Criteria

Participants eligible for the trial must comply with all of the following criteria at randomisation:

1) Aged 18-70 years.
2) Right handed
3) Meet criteria for overweight or obesity (BMI $\geq$25kg/m^2).
4) Meet diagnostic criteria for full-syndrome BED diagnosis according to the Diagnostic and Statistical Manual 5th Edition (2013).
5) Normal or corrected to normal vision.
6) Access to a laptop or desktop computer with a webcam.

4.3.2.3 Exclusion Criteria

1) Insufficient knowledge of the English language.
2) Pregnancy or suspected pregnancy.
3) Enduring COVID-19 related symptoms which may alter eating behaviour, including loss of taste or smell.
4) Current significant or unstable medical or psychiatric disorder needing acute treatment in its own right.
5) A lifetime diagnosis of substance dependence, psychosis, bipolar disorder, or borderline personality disorder.
6) Developmental or neurological disorder (e.g., dementia, attention deficit hyperactivity disorder, autism spectrum disorder).
7) Psychotropic medication other than a stable dosage of an antidepressant (e.g., selective serotonin reuptake inhibitor) for at least 14 days prior to study enrolment.
8) Non-removable metal parts in the area of the head (excluding dental work).
9) History of epilepsy or migraine.
10) Use of a pacemaker.

We will report the number of participants excluded, with reasons, and the number who decline consent or withdraw from the study, with reasons where provided.

4.3.3 Sample size

As TANDEM aims to establish feasibility rather than between-group differences, an a priori sample size calculation is not necessary. Guidance suggests that, where available, sample size should be based on previous feasibility or pilot studies of a similar intervention, or with a similar primary outcome measure or trial design. Where this information is lacking, it is argued that a total sample between n=12 and n=50 is sufficient for robust assessment of feasibility outcomes (Eldridge et al., 2016). Previous comparable trials in BED included 20 participants in each trial arm (e.g., Gordon et al. (2019) and Giel, Schag, et al. (2022)). As this trial includes four arms, we have chosen a target end study sample size of n=80. Assuming the attrition to follow-up rate is ~10% (as found in previous recent BED treatment trials, e.g., Schag et al. (2019)), we will recruit an actual sample size of 88 (22 participants/group).

4.3.4 Randomisation

The study will use a randomised controlled design, stratified by age, gender and BMI. Participants will be randomly allocated to a study group in a 1:1:1:1 ratio. Randomisation will be completed using the Sealed Envelope Simple+ randomisation service (https://www.sealedenvelope.com/). After completing the T2 assessment, participants in the waiting control arm will be offered ABMT.

4.3.5 Blinding and protection against bias

For pragmatic reasons, single blinding will be implemented for ABMT + real tDCS and ABMT + sham tDCS groups. As such, participants in tDCS treatment groups will be blinded to real/sham allocation, but the researcher who leads treatment and conducts assessments will be unblinded. A validated protocol for sham stimulation will be used to deliver sham treatment; in the sham condition, tDCS electrodes will be properly mounted over the right and left DLPFC, and a 2mA current will be applied for 60 seconds at the beginning and end of each session. During the first and final 60 seconds of each session, no ABMT will be completed. Therefore, participants who receive sham will perceive typical sensations of tDCS (e.g. tingling), but will be unaffected by the stimulation. To assess if blinding was successful, participants will be asked to guess which condition they believe they have received and indicate how certain they feel about this. Once T2 and, where relevant

the optional semi-structured interview about the treatment experience, are complete, participants will be unblinded. Those who receive sham treatment will not be offered any additional treatment. Blinding will not be implemented for ABMT only and waiting conditions.

The single-blind study design increases risk for experimenter bias. To protect against bias, self-report questionnaires (as opposed to interviews) will be used to assess clinical outcomes, including episodes of binge eating. All outcome measures will be collected online using either Qualtrics^{XM} for questionnaire measures, or Gorilla^{TM} or Inquisit Millisecond for neurocognitive task measures. As such, the experimenter will have no influence on participant responding or task performance. Semi-structured interviews about the treatment experience will be conducted before participants are unblinded and by independent investigators who are naïve to real/sham allocation.

4.3.6 Intervention

Participants will complete 10 sessions of tele-supervised treatment over 2-3 weeks (i.e., week daily sessions until 10 sessions have been completed). Sessions will involve either concurrent ABMT and real/sham tDCS, or ABMT only. Participants in the waiting control arm will receive ABMT after completion of the T2 assessment.

4.3.6.1 Attention Bias Modification Training

ABMT aims to train participants to 'look towards' low-calorie food and 'look away' from high-calorie food using a modified version of the anti-saccade task by Werthmann et al. (2014). Training is completed on a personal laptop or desktop computer and lasts 10-15 minutes with breaks. Participants completing concurrent treatment (i.e., ABMT + real/sham tDCS) will begin ABMT five minutes after starting the stimulation. They will also be instructed to rest while waiting to begin and after completing the training.

ABMT Paradigm

The modified task consists of 360 trials. Of these, 180 require participants to look towards low-calorie foods, and 180 trials require participants to look away from high-calorie foods. At the beginning of each trial, a black fixation point appears for 100ms, followed by a red or blue fixation point (500ms). A blue point indicates that a

pro-saccadic eye movement is required (i.e., look towards the food picture which appears after the fixation point), whereas a red point requires an anti-saccadic eye movement (i.e., direct the gaze away from the food picture which appears after the fixation point). Low-calorie cues are always preceded by a blue dot and high-calorie food cues are always preceded by a red dot. A blank screen is inserted for 200ms between the fixation point and the stimulus presentation. The pictorial stimulus (a high- or low-calorie food picture) then appears on either the left or the right side of the screen for 500ms. Inter-trial interval is 1300ms. Trials will be presented in a random order across three blocks, each including 120 trials. See Figure 4.1 for an example of a pro-saccade and anti-saccade stimulus presentation.

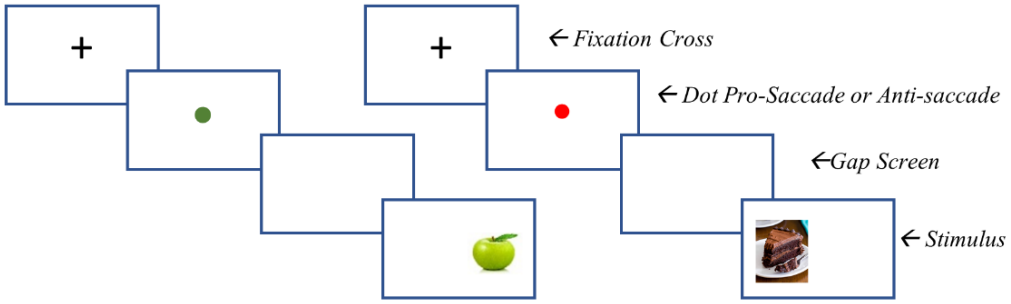
Stimuli

Pictorial stimuli are 30 low-calorie food and 30 high-calorie food pictures, which are visually matched for brightness, colour, and complexity, taken from Werthmann et al. (2014). Each image is presented twice in each block, once on the left side of the screen and once on the right side of the screen (in a counterbalanced order), resulting in a total of 360 training trials (30 food stimuli + 30 non-food stimuli × 2 positions × 3 blocks).

Response and Feedback

In addition to directing their gaze towards or away from the stimulus presented, participants will be instructed to press the arrow key which corresponds with the direction of their gaze. Response latencies will be recorded to monitor accuracy and provide participants with feedback. For each block, number of correct responses will be summed and presented as percentage score to the participant.

Figure 4.1. ABMT stimulus presentation.



Note: Left = pro-saccade stimulus presentation (i.e., participant is to look towards the food image presented). Right = anti-saccade stimulus presentation (i.e., the participant is to move their gaze away from the stimulus).

4.3.6.2 Self-Administered Transcranial Direct Current Stimulation

Participant administered tDCS will be delivered using the Newronika HDC system (Figure 4.2). The Newronika system consists of an easy to use, lay-person friendly stimulator, a programming device used by the researcher to securely set stimulation parameters, and a customisable MindCap electrode placement system which ensures simple, safe, and reliable placement of the anode and cathode over the right and left DLPFC. Stimulation will be delivered at a constant current of 2 mA (with a 30 second fade in/fade out) for 20 minutes. This tDCS montage has been used in studies of food craving, BN, and BED (Giel, Schag, et al., 2022; Gordon et al., 2019; Kekic et al., 2017). As with real tDCS, sham stimulation will run for 20 minutes however, participants will not receive active stimulation for the full 20-minute period. Instead, sham participants will receive 60 seconds of stimulation at the start ("ramping up") and the end ("ramping down") of the stimulation period.

Figure 4.2. Equipment for tDCS self-administration.

4.3.6.3 Rationale for Session Number and Frequency

Although consensus around the optimal number of ABMT sessions is lacking, a review of meta-analyses of CBM concluded that the number of sessions appears to moderate outcomes, with higher session numbers being associated with greater change in cognitive bias (Jones et al., 2016). In line with this, Beard (2011) found that as session number increased, so did the potency of the effect of CBM on symptoms in depression, anxiety, and addiction disorders. However, this effect

appeared to stabilise after 10 sessions. Therefore, 10 sessions may be the optimal dose for ABMT.

With regards to tDCS, although there is a similar lack of consensus about the optimal treatment parameters, it is broadly accepted that multiple sessions are needed to achieve lasting therapeutic effects (Brunoni et al., 2019; Moffa et al., 2018). The vast majority of multisession studies in psychiatric disorders have applied 10-sessions of tDCS once daily over 2-3 weeks (Moffa et al., 2018). Thus, the choice of 10 sessions is also supported by the literature on tDCS use in psychiatric disorders.

4.3.6.4 Safety Procedures

Published guidance for ensuring participant safety during self-administration of tDCS will be adhered to (Knotkova et al., 2019). This guidance is as follows: First, training and supervision should be provided to those self-administering tDCS. In TANDEM, all participants will be trained in safe tDCS self-administration, and all treatment sessions will be supervised via video-call. Second, the tDCS equipment used must be intended for home use by the lay community. We will use the Newronika HDC stimulator and MindCap electrode placement system which is CE marked for supervised home use in the UK and Europe. This equipment is pre-programmed by the researcher, simple to use, and includes features which prevent misuse (e.g., the researcher can set a minimum time between treatment sessions, and/or set a maximum number of sessions before re-calibration by the researcher). Third, care must be given to the participant's capacity for self-administration. Prior to beginning treatment, the TANDEM researcher will assess each participant's ability to self-administer tDCS safely. Where necessary, additional training will be provided. Participants who cannot safely self-administer tDCS after training will be withdrawn from the study, and the reason for their withdrawal will be reported. Fourth, tDCS tolerance and adverse events must be assessed at each session. Consistently, process outcomes will monitor tDCS tolerance and adverse events at each treatment session (see "Outcome Assessment" for more details). In addition, during or near to the final (T2) assessment, tDCS tolerance and adverse events will be assessed in an optional semi-structured interview about the treatment experience.

4.3.6.5 Concomitant care

As the trial focusses on feasibility rather than efficacy, participants will be allowed to receive other parallel treatments for their ED. Concurrent use of psychoactive medications (excluding neuroleptics or benzodiazepines) will be allowed, providing the dose has been stable for at least 14 days prior to baseline assessment.

4.3.7 Trial procedure

The individual participant timeline is illustrated in Figure 4.3. Study duration for each participant is 8 weeks. All participants will partake in assessments at each of the three time points; baseline (T0), post-treatment (T1) and follow-up (T2). Each assessment will be completed via videoconferencing (i.e., participants complete both assessments and treatment at home using a laptop or desktop computer with a webcam). Questionnaire measures will be completed online using Qualtrics^{XM} and neurocognitive tasks will be completed online using either Gorilla^{TM} or Millisecond by Inquisit^{TM}. Assessments will take place between 9am and 5pm, and participants will complete their assessment at the same time of day for the duration of the trial (i.e., each participant will complete each assessment at the same time of day).

Informed consent will be provided via an online consent form (Qualtrics^{XM}). Once completed, potential participants will be screened over the phone for inclusion in the study. At screening, BED diagnosis is confirmed using a standardised interview (Eating Disorders Diagnostic Screen; Stice et al. (2000)). Physical and psychiatric comorbidities, current medications, and tDCS safety are assessed using a general health questionnaire developed for the purpose of screening. Eligible participants then complete the baseline (T0) assessment. After baseline assessment, participants are randomised to one of four groups: (1) ABMT + real tDCS, (2) ABMT + sham tDCS, (3) ABMT only, or (4) wait-list control group. Intervention groups will then complete 10 sessions of treatment, up to 5 sessions/week, across 2-3weeks. Treatment sessions will take place at the same time of day each day, and participants will be asked not to eat or drink anything for at least 2 hours prior to each session. The waitlist control group will receive no experimental treatment during this time. All participants will complete the post-treatment assessment (T1) after the 10th (final) session of treatment or 2-weeks of waiting, and the follow-up assessment (T2) 6-

weeks after completing treatment, or after 8-weeks of waiting. After completing the final (T2) follow-up, waiting control participants will receive ABMT.

Figure 4.3. Participant Timeline

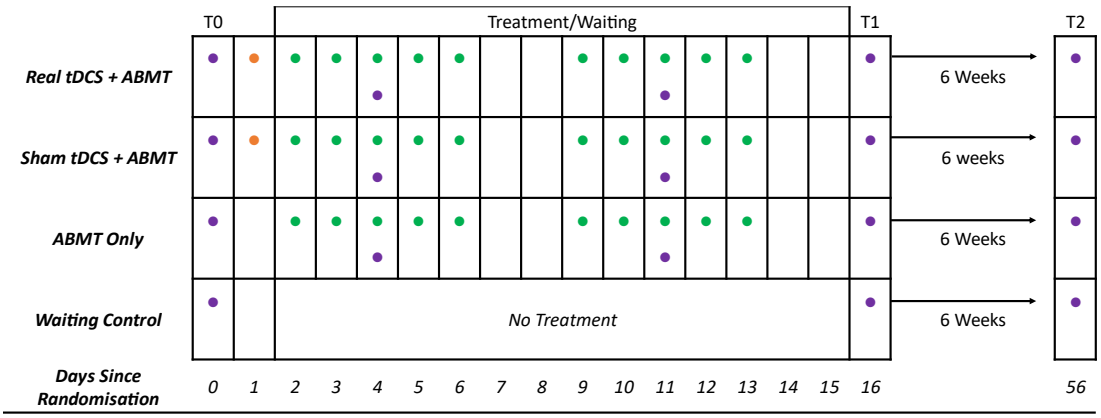


Figure Legend. ● = *tDCS self administration training,* ● = outcomes assessment, ● = treatment session.

4.3.8 Outcome assessment

4.3.8.1 Primary outcomes

The primary clinical outcome will be the change in monthly episodes of objective binge eating from baseline (T0) to follow-up (T2), as measured by the Eating Disorders Examination Questionnaire [EDE-Q, Fairburn and Beglin (2008)]. Episodes of objective binge eating in the previous month will be drawn from items 13 and 14 of the EDE-Q. Item 13 asks, "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?" and item 14 follows with: "On how many of these times did you have a sense of losing control over your eating?". Responses to item 14 indicated the number of episodes of objective binge eating in the previous 4 weeks." Medians and rate ratios (with confidence intervals) will be reported, and these will inform the minimum sample size required for a fully powered large-scale RCT. Rates for recruitment and retention to 8-week follow-up will also be reported to provide insight into the time and resources needed for a larger trial.

Intervention acceptability will be assessed in two ways. First, by asking participants the following two questions at post-treatment (T1) and follow-up (T2) assessments: (1) "If you could continue with this treatment, would you?" (Yes/No) and "Would you recommend this treatment to a friend who was struggling with binge eating?" (Yes/No). The intervention will be viewed as acceptable if at least 75% of those who

receive the real concurrent treatment indicate that they would continue the intervention if given the opportunity and/or if 75% would recommend the treatment to a friend. Second, at or near-to the final (T2) assessment, participants will be invited to complete an optional semi-structured interview about the treatment experience. This will provide qualitative data which will give insight into (a) whether participants viewed the treatment as acceptable and (b) why/why not. Interviews will be recorded, transcribed, and analysed using thematic analysis.

Feasibility will also be assessed by looking at participant ratings of tDCS tolerability. Participants who receive tDCS will complete a 10-point visual analogue scale (VAS) of tDCS discomfort after each session. We will then take the average of ratings across the ten sessions for each participant and use this to assess the average rating for tDCS related discomfort for the real tDCS + ABMT group. The intervention will be considered well-tolerated if this number is ≤4 (i.e., mild discomfort). Prior to beginning each tDCS session, participants will also report any side effects they have experienced since their previous session. The type and frequency of side effects will be reported for consideration.

4.3.8.2 Secondary outcomes

Secondary outcomes will be assessed using validated self-report instruments and neuropsychological tasks. Change in score/performance from baseline (T0) to post-treatment (T1) and follow-up (T2) will be examined by looking at within- and between-group effect sizes and standard deviations. These data will inform outcome measure selection for a future large-scale RCT.

4.3.9 Outcome measures

See Table 4.1 for a summary of the measures collected at each timepoint and Appendix H. for copies of each measure.

4.3.9.1 Questionnaire measures

Participants will complete a battery of questionnaire measures at each assessment (T0, T1 and T2). These will assess ED psychopathology [Eating Disorder Examination Questionnaire (Fairburn & Beglin, 2008)], general psychopathology [Depression, Anxiety and Stress Scale – 21 item version (Lovibond & Lovibond, 1995)], craving for food [Food Craving Questionnaire – trait version (Cepeda-Benito

et al., 2000)], ED related clinical impairment [Clinical Impairment Assessment (Bohn & Fairburn, 2008)], emotion dysregulation [Difficulties with Emotion Regulation Scale – 16 item version (Bjureberg et al., 2016)], and impulsivity [Barratt Impulsiveness Scale (Patton et al., 1995)]. Self-reported weight and height will be used to calculate BMI.

4.3.9.2 Task measures of neurocognition

Attention bias towards high-calorie foods will be assessed using the visual probe task described in Mercado, Werthmann, et al. (2020). In TANDEM, as participants will be taking part from home, webcam based eye-tracking technology (as opposed to specialist lab-based eye-tracking equipment) will be used to record eye movements.

Food-related attention will be assessed using the food-specific attention network task described in Hege et al. (2017) and in Mercado, Werthmann, et al. (2020). This task examines three components of attention (alerting, orienting, and executive function) using food (low- and high-calorie) and non-food picture stimuli.

Working memory will be assessed using the n-back task described in (Meiron & Lavidor, 2013). Accuracy (% correct responses) and reaction time for correct responses (ms) will be reported.

Affective inhibitory control will be assessed using the Face Affective Go/No-Go task from the EMOTICOM neuropsychological test battery (Bland et al., 2016). Error rate and latency will be used to estimate inhibitory control, and reaction times will be used to calculate affective bias scores.

Cognitive flexibility will be assessed using the Wisconsin Card Sorting Test (Kongs et al., 2000). Difficulties with set-shifting will be reflected in perseverative errors, thus, higher scores on this test indicate poorer performance.

Preference for immediate versus delayed rewards will be assessed using the delay discounting task described by Kirby and Maraković (Kirby & Maraković, 1996). Modelling techniques are used to fit participant responses to the function that relates time to discounting. This produces a temporal discounting curve. The rate at which delayed rewards are discounted will be derived by calculating the area under the curve, and steeper discounting will be reflected by a smaller area under the curve (Myerson et al., 2001).

4.3.9.3 Optional semi-structured interview

All participants (i.e., including those who received ABMT only) will be invited to complete a semi-structured interview about the treatment experience. This interview, developed for the TANDEM trial, was based on previous semi-structured interviews about tDCS treatment by Gordon, Williamson, et al. (2021) and Smits et al. (2021). Questions examined seven domains of acceptability: affective attitudes, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness, and self-efficacy. Interview prompts are presented in Appendix H.13.

4.3.9.4 Within-session measures

At each treatment session participants will complete measures of current symptoms and, where relevant, tDCS related discomfort. Before each treatment begins, participants will complete an online "check in" questionnaire which asks about episodes of binge eating since their previous session and, where relevant, adverse events/side effects that may be related to tDCS. They then complete 10-point visual analogue scales (VAS) assessing current hunger, feeling of fullness, craving for food, urge to binge, level of tension, level of stress, level of discomfort, and feeling of low mood. At the end of each session, participants complete a "check-out" questionnaire which repeats VAS measures and, where relevant, asks about tDCS related discomfort during the session.

4.3.10 Data analysis

The primary analysis will use the number of episodes of binge eating in a Poisson regression model with baseline adjustment. Descriptive statistics will be used to assess recruitment and retention rates, intervention adherence, and the quality and completeness of the data. In secondary analyses, a mixed model approach will be used to analyse the effect of treatment on primary (PO) and secondary outcomes (SOs), with baseline adjustment. To examine the whether the effect of treatment is different for different levels of overweight or obesity, BMI will be included in the model as an interaction effect. Effect sizes will be analysed and reported for PO and SOs. For the Poisson regression, rate ratios will be reported. For binary outcomes, odds ratios will be reported. For quantitative outcomes, standardized differences will be reported. Primary parameters will be time vs. treatment interactions at both timepoints after baseline. P-values will be reported but for exploratory purposes only

(i.e., they will not be interpreted to accept or reject the null hypothesis). The analyses will be done in the intent to treat population, which is defined by including all patients with baseline assessment. Outcome data already obtained for participants who discontinue or deviate from the intervention protocol will be kept and analysed. Analyses will be conducted using RStudio (R: Core Team, 2020). Effect sizes for change scores will be reported using Hedge's *g:* a measure of effect size which provides more stringent control for inflation in studies using a small sample size (e.g., $n < 20$). The effect size expresses the difference of the means in units of the pooled standard deviation. Cohen (1977) proposed a "rule of thumb" for interpreting Hedge's *g:* effect sizes ≤ 0.2 are small, ≤ 0.5 are moderate, ≤ 0.8 are large.

Table 4.1 Summary of outcome assessment by visit

	Screening	T0	In Treatment	T1	T2
Eating Disorder Diagnostic Screen	X				
TDCS Safety Screen	X				
General Health and Lifestyle Questionnaire	X				
Demographics		X			
Eating Disorder Examination Questionnaire		X		X	X
Depression, Anxiety, Stress Scale		X		X	X
Food Craving Questionnaire – Trait Version		X		X	X
Clinical Impairment Assessment		X		X	X
Difficulties in Emotion Regulation Scale		X		X	X
Barrett Impulsiveness Scale		X		X	X
Visual Probe Task		X		X	X
Food Attention Network Task		X		X	X
N-Back Task		X		X	
Wisconsin Card Sorting Task		X		X	
Delay Discounting Task		X		X	
Affective Go/No-Go Task		X		X	
VAS Measures		X	X	X	X
Assessment of tDCS Discomfort/Side			X		
Semi-structured interview about treatment					X

4.3.11 Patient and public involvement

In our previous trial of tDCS enhanced CBM in BED, a subset of participants completed a semi-structured interview about their treatment experience (Gordon et al., 2019). These interviews included a question about participant views about future directions for tDCS in BED. While these responses did not refer directly to at-home treatment, participants described practical barriers to accessing treatment (e.g., caring responsibilities, time pressures, and travel burden). From these responses, we inferred that participants would welcome investigation into at-home treatment. Prior to submitting the study protocol for review by the research ethics committee, ten randomly selected participants from our previous trial were invited to provide feedback about the proposed intervention procedures, and the objectives for the research. Eight participants responded with constructive feedback which was incorporated into the study before ethics approval was awarded.

Participant facing forms were also reviewed by people with lived experience of mental health problems and their carers via the South London and Maudsley's Feasibility and Acceptability Support Team for Researchers (FAST-R).

4.3.12 Ethical considerations

The TANDEM trial was awarded favourable opinion by the London-Fulham NHS Research Ethics Committee on the 6th of August 2020 (REC Reference 20/LO/0936). Approval to begin the trial was granted by the Health Research Authority (HRA) on the 6th of August 2020. All trial participants will provide written informed consent prior to inclusion into the study and may withdraw from the trial at any point, without consequence or giving a reason.

4.4 Discussion

The TANDEM trial will be among the first feasibility studies of concurrent tDCS with cognitive training in BED (see also Gordon et al, 2020; Giel, Schag et al., 2022). As such, we expect it will contribute new information and will inform the continued development of neurobiologically informed approaches to BED treatment. Indeed, should this trial evidence that concurrent tDCS and ABMT is feasible and acceptable, a large-scale trial with long-term follow-up will be needed to evaluate treatment effectiveness.

The design has several strengths. While most studies of tDCS use convenience samples from healthy populations, TANDEM will use a clinical sample who meet DSM-5 criteria for BED. Second, by bringing brain-based treatment into the home, TANDEM overcomes a number of barriers to treatment cited by participants in previous studies (Dalton et al., 2022; Gordon, Williamson, et al., 2021). Moreover, we will increase access to treatment during a time of elevated uncertainty and compromised access to conventional care (i.e., during the coronavirus pandemic). In fact, in a letter to Brain Stimulation, Caulfield and George (2020) called for this type of approach, saying that the time is ripe for investigating at home neurotherapeutics, and that tDCS is a prime candidate. Third, we have tested our CBM intervention (ABMT) in trials involving adults with obesity (Mercado, Werthmann, et al., 2020) and anorexia nervosa (Mercado, Schmidt, et al., 2020): in this latter case, training focused on altering avoidance of food, as opposed to bias towards high-calorie foods. As such, we have a useful preliminary understanding of the therapeutic effects of ABMT in populations with EDs and disordered eating behaviours, and a good understanding of how participants view the treatment (i.e., acceptable, accessible, and credible). Fourth, we have chosen a primary outcome with high clinical relevance (i.e., monthly episodes of binge eating), and, unlike many studies which examine short-term intervention effects, we have incorporated a comparatively long follow-up period (6-weeks post-treatment end). This will allow us to examine the maintenance of any therapeutic effects observed immediately post-treatment and allow time for more gradual changes to emerge.

There are some challenges for the TANDEM trial. TANDEM is/has been conducted during the coronavirus pandemic (COVID-19) and it is possible that there may be a negative COVID-related impact on recruitment and retention. In response,

TANDEM has adopted a fully remote design (i.e., participants complete all components of treatment and research participation from home). We expect that this may mitigate the negative impact of COVID on recruitment however, by adopting a fully remote design, TANDEM has sacrificed some of the advantages of conducting research in the lab (e.g., access to state-of-the art eye tracking equipment, controlled testing environments, and reduced reliance on self-report data). In publications arising from this trial, we will comment on the quality and completeness of the data collected to assist with future decisions about trial design. As the focus for this trial is feasibility, and we expect widespread infection with COVID-19 during the trial period (12 months), participants will not be excluded from taking part if they report recent illness with COVID-19. Participants will be asked about any illness during the previous six months at screening, and numbers with recent COVID-19 will be reported in publications resulting from this trial. In addition, those reporting long-COVID, or post-COVID alterations to taste and smell will be ineligible to take part due to the possible effects of these symptoms on eating behaviour. Finally, to minimise attrition, we have chosen to collect only a subset of outcome measures at follow-up. As such, we will not be able to comment on change from baseline to follow-up for some secondary neurocognitive outcomes.

In TANDEM, participants will complete treatment at the same time of day each day, but they may choose the time for treatment which works best for them. We expect that this flexibility around treatment session time may enhance feasibility and promote adherence to the treatment protocol. However, it is possible that intervention effectiveness may vary with time of administration; for example, it is possible that the effects on eating behaviour may be amplified when the intervention is delivered shortly before meal times, or at times when a person would often experience objective binge episodes. Should the findings from the TANDEM trial indicate that tDCS with ABMT is feasible and well tolerated, it may be encouraged that future feasibility studies assess whether being more prescriptive about time for treatment compromises treatment adherence and/or trial feasibility, and for fully powered trials to consider the effect of time of treatment on intervention efficacy.

We expect that the TANDEM trial will provide a valuable contribution to the literature on concurrent tDCS and CBM treatments for EDs, and that the data collected will provide a foundation for future related trials. Moreover, we hope that

TANDEM will shed light on the potential for bringing NIBS treatments into the home so that we can continue increasing access to novel treatments for psychiatric disorders.

4.4.1 Trial progress

Recruitment commenced in March 2021 and ended in February 2022. Data collection will be completed by June 2022. Amendments to the study protocol will be reported in publications of study outcomes.

Chapter 5. Clinical and feasibility outcomes from the TANDEM trial of concurrent transcranial direct current stimulation and attention bias modification training in binge eating disorder

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Author contribution: The study was conceptualised and designed by the candidate (Michaela Flynn), Professor Ulrike Schmidt and Professor Iain Campbell. The candidate obtained ethical approval from the NHS Research Ethics Committee and the Health Research Authority. The candidate performed all aspects of recruitment, delivery of the trial interventions, data collection, data entry, and data analysis. The candidate drafted the chapter with constructive feedback from her supervisors, Professor Ulrike Schmidt and Professor Iain Campbell.

Abstract

Background: Binge eating disorder (BED) is a common and disabling psychological disorder associated with elevated craving for food, emotion dysregulation and compromised cognitive control. Transcranial direct current stimulation (tDCS) and attention bias modification training (ABMT) are safe, scalable brain-directed treatments that produce modest improvements in BED symptoms, and emerging evidence suggests that their efficacy may be enhanced when these interventions are combined. We conducted a randomised control trial of concurrent self-administered tDCS with ABMT in adults with BED to assess trial feasibility and intervention acceptability, and to obtain preliminary data relating to intervention efficacy.

Methods: This study was a randomised sham-controlled feasibility trial. Eighty-two participants with BED and a body mass index (BMI) of ≥ 25 kg/m^2 were randomly allocated to one of four groups: real tDCS with ABMT, sham tDCS with ABMT, ABMT only, or 6-week waiting list control. Intervention groups received 10 sessions of their allocated treatment over 2-3 weeks. tDCS was administered using a bilateral (anode right/cathode left) montage targeting the dorsolateral prefrontal cortex and 2mA stimulation intensity. Outcome measures were assessed at baseline, post-treatment and 6-week follow-up.

Results: Recruitment rates (6-7 monthly) and retention to follow-up rates (82.9%) exceeded pre-specified criteria for feasibility, and intervention acceptability ratings were high. Accordingly, treatment completion rates were high for all intervention groups (98.7%). Between-group effect sizes for change scores revealed that all three interventions reduced episodes of objective binge eating, eating disorder symptoms and related psychopathology, relative to waiting list control (medium-to-large effect sizes). Small-to-medium effect sizes for change scores favoured real tDCS with ABMT, as opposed to ABMT only or sham tDCS with ABMT, suggesting that the real intervention may produce superior outcomes.

Conclusion: Findings demonstrate that the study protocol is feasible, and that the intervention is acceptable. Preliminary findings relating to clinical efficacy were also promising, however, fully powered trials are needed to substantiate these findings.

5.1 Introduction

This chapter presents key findings from the randomised controlled feasibility trial of self-administered transcranial direct current stimulation (tDCS) with attention bias modification training (ABMT) in binge eating disorder (BED) (see Chapter 4 for protocol). As outlined previously in this thesis, psychotherapy, most commonly cognitive behaviour therapy, is presently recommended for the treatment of BED however, outcomes from therapy are sub-optimal for a substantial proportion of patients; for example, a meta-analysis found that approximately half of patients continue to struggle with episodes of objective binge eating after treatment ends (Hilbert et al., 2020). This highlights the need to develop new treatments for BED.

Recent research has highlighted that compromised cognitive control, as demonstrated by emotion dysregulation and attention bias towards food, may be central to the aetiology and maintenance of BED (Giel, Bulik et al., 2022). Models of BED frequently posit that negative affect and difficulties regulating negative emotions are core features of BED, with many highlighting the role of negative affect as a reliable trigger for objective binge eating behaviour (e.g., Leehr et al., 2015). Accordingly, studies have demonstrated that individuals with BED have difficulty implementing explicit-controlled (i.e., top-down) forms of emotion regulation, such as reappraisal (e.g., Dingemans & van Furth, 2012), and that they make use of these adaptive emotion regulation strategies less frequently than healthy controls (Gianini, et al., 2013; Harrison, et al., 2016; Lavender et al., 2015; Lavender et al., 2014). As such, compromised cognitive control may be a key maintenance mechanism in BED.

Relatedly, food-related attention biases have been described in BED (Albery et al., 2016; Schag et al., 2013; Stojek et al., 2018). Indeed, studies have suggested that attention bias towards food may distinguish BED from obesity. For example, in our cross-sectional study of attention bias towards food in adults with obesity with and without BED (Chapter 3) we observed that participants with BED showed a generalised pattern of attention bias towards food (regardless of calorie content), whereas participants without BED showed a bias towards high-calorie, but not low-calorie, food. These findings may suggest that food, in general, captures attention in BED in a "bottom-up" stimulus-driven fashion, and that "top-down" cognitive control resources may be insufficient to re-orient attention in a goal-directed way.

Indeed, this may contribute to high levels of craving, strong motivation to eat and loss-of-control eating behaviour in BED (Stojek et al., 2018).

Brain-directed treatments, including ABMT and tDCS, are emerging treatments which may directly influence cognitive control. Findings from preliminary trials suggest that ABMT may produce a small, yet significant, reduction in high-calorie food consumption and craving in healthy adults (Turton, et al., 2016) and in individuals with normal weight and overweight/obesity (Fodor et al., 2017; Mercado et al., 2023) and adults with BED (Boutelle, et al., 2016; Schmitz & Svaldi, 2017). Similarly, tDCS, a form of non-invasive brain stimulation, has shown therapeutic potential in BED. Single-session pilot studies have shown that tDCS targeting the dorsolateral prefrontal cortex (DLPFC) can produce short-term (up to 24 hour) improvements in eating disorder (ED) psychopathology, reduce craving for food and reduce objective binge eating behaviour (Burgess et al., 2016; Kekic et al., 2017; Max, et al., 2021) and multi-session studies have shown that 10 sessions of tDCS alters attention bias towards food, craving for food, and cognitive flexibility (Afzali, et al., 2021).

Importantly, several trials have reported superior outcomes from tDCS treatment when it is combined with another intervention which activates disorder-related neural networks (Gordon, *unpublished thesis;* Heeren, et al., 2015; Heeren et al., 2017; Moffa et al., 2018). For example, a recent feasibility study in BED demonstrated that when combined with approach bias modification, six sessions of tDCS may produce substantial reductions in objective binge episodes for up to seven weeks post-treatment (Gordon, *unpublished thesis).* As a result, superior outcomes from treatment may be achieved by combining tDCS with ABMT in BED. Moreover, with the recent arrival of tDCS devices intended for supervised self-administration, both interventions can now be safely provided in the home, thereby increasing their accessibility and scalability. Accordingly, this chapter outlines the feasibility and clinical outcome from a randomised sham-controlled feasibility trial of 10-sessions of self-administered tDCS with ABMT in BED (the TANDEM trial).

5.2 Study aims and hypotheses

The primary objective of the TANDEM trial was to evaluate protocol feasibility and intervention acceptability. In doing so, we aimed to acquire key information to inform the design of a large-scale randomised controlled trial (RCT).

Aims:

1. To estimate the rate ratio for the proposed primary outcome, change in the number of monthly episodes of objective binge eating from baseline to follow-up.
2. To assess recruitment, attendance, and retention rates.
3. To evaluate participant views of treatment acceptability and tolerability.
4. Determine the best instruments for measuring primary and secondary outcomes in a full trial by examining the quality, completeness, and variability in the data.
5. To estimate between-subject effect sizes and confidence intervals for clinical outcomes to inform sample size calculation for a future large-scale RCT.

Hypotheses:

We expect that treatment (i.e., real tDCS with ABMT, sham tDCS with ABMT and ABMT only) will achieve therapeutic effects by post-treatment (i.e., reduced monthly episodes of objective binge eating, ED symptom severity, trait craving for food, general psychopathology and ED related impairment) relative to WL, and that these will endure to follow-up. However, therapeutic effects will be most substantial in BED (as demonstrated by larger effect sizes for change scores relative to WL). Specifically,

5.3 Methods

A detailed overview of the study design, participants, intervention, and outcome assessments is provided in the TANDEM protocol paper presented in Chapter 4 (Flynn et al., 2022). The TANDEM trial was given favourable opinion by the London and Fulham NHS research ethics committee (REC Reference 20/LO/0936) and approval to begin the trial was granted by the Health Research Authority (HRA) on the 6th of August 2020.

5.3.1 Design, participants, and setting

TANDEM was a single-blind randomised sham-controlled study with four parallel arms: (1) real tDCS+ABMT, (2) sham tDCS+ABMT, (3) ABMT only, (4) waiting control (WL). Outcomes were assessed at baseline (T0), post-treatment (T2; immediately after treatment completion or 2-weeks after baseline for WL) and at follow-up (T2; 6-weeks after end-of-treatment or 8-weeks after baseline for WL).

Participants were right-handed community-dwelling adults (≥18 years old) who met criteria for overweight or obesity (BMI ≥ 25 kg/m^2) and met criteria for BED diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (5th Edition) [DSM-5]. To ensure participants were able to complete treatment and research-related activities, they were also required to have normal or corrected to normal vision and access to a laptop or desktop computer with a webcam. Main exclusion criteria were contraindications to tDCS (e.g., history of seizures or migraines). Participants were recruited from the community via online advertisements and from the outpatient ED service at South London and Maudsley NHS Foundation Trust.

Potential participants first provided written informed consent, then they were screened over the phone to determine eligibility. Eligible participants were invited to complete the baseline assessment after which they were randomly allocated to one of the four study arms.

Participants took part in TANDEM remotely, using a personal laptop or desktop computer with a webcam (i.e., all treatment and research activities were completed from home with researcher support provided via video-call). All were asked to complete TANDEM activities in a quiet space where they were not likely to be

disturbed, and where they felt comfortable speaking freely about their eating and mental health.

5.3.2 Randomisation and blinding

Participants were randomised using the Sealed Envelope Simple+ randomisation service (https://www.sealedenvelope.com/). Participants were allocated at a ratio of 1:1:1:1 to one of the 4 trial arms using a restricted randomisation algorithm which stratified by age, BMI, and gender. TANDEM used single blinding for tDCS trial arms. As such, only participants were blind to real/sham tDCS treatment allocation. To assess if blinding was successful, participants were asked to guess which condition they believed they received and to indicate how certain they felt about this. Participants were unblinded after the follow-up assessment. Those who received ABMT with sham tDCS were not offered any additional treatment.

5.3.3 Intervention

The intervention is described in detail in Chapter 4. In brief, participants received 10 sessions of tele-supervised treatment over 2-3 weeks (i.e., week daily sessions until 10 sessions have been completed). Depending on treatment group allocation, sessions involved either concurrent ABMT and real/sham tDCS, or ABMT only. Each session lasted 30 minutes, including preparation time and time spent completing within-session outcome measures. During ABMT, participants were trained to 'look towards' low-calorie food and 'look away' from high-calorie food using a modified version of the anti-saccade task (Mercado, et al., 2020; Werthmann, et al., 2014). ABMT was completed online using a personal laptop or desktop computer and lasted approximately 10-15 minutes with breaks.

Participants in real and sham tDCS groups received stimulation while completing ABMT. Stimulation started five minutes before ABMT so that stimulation and ABMT concluded approximately simultaneously. In real tDCS, stimulation was self-administered using the MindCap^{TM} (Figure 4.2). The anode was placed over the right DLPFC, and the cathode was placed over the left DLPFC, and stimulation was delivered at an intensity of 2mA for 20 minutes with a 60-second fade in/fade out period. In sham, participants set up electrodes in the same way and received active stimulation during the fade in/fade out periods only (i.e., 2 minutes total). This is a validated protocol for sham stimulation in which the participant experiences typical

sensations associated with tDCS (e.g., tingling) but does not receive stimulation with sufficient intensity or duration to alter cortical excitability.

5.3.4 Outcomes

Primary outcomes related to trial feasibility, intervention acceptability, and therapeutic effects. The primary feasibility outcomes were recruitment, attendance, and retention rates. To judge whether/how to proceed with a future definitive trial, we pre-specified two criteria: first, randomisation of at least 5 participants, on average, each month over 12 consecutive months, and second, retention to follow-up rates of ≥75%. We did not prespecify any treatment session attendance rates required for progression to a full trial, however these would also guide a decision about the feasibility of a future trial. For real/sham tDCS participants, we also assessed blinding success at post-treatment and follow-up. Participants completed a forced choice binary question, "do you think you received real or sham tDCS?", followed by a 10 point visual analogue scale (VAS) asking, "how confident do you feel about your choice?", where 0 meant 'not at all confident' and 10 meant 'certain'. Blinding was considered successful if participants correctly guessed their allocation at a rate comparable to chance.

Acceptability was assessed in two ways: first, at post-treatment and 8-week follow-up using two binary (yes/no) questions about (a) whether the participant would continue the intervention if they could, and (b) whether they would recommend the intervention to a friend struggling with binge eating. Pre-specified endorsement rates of at least 75% were needed to conclude that participants viewed the intervention as acceptable. Second, after each treatment session, participants who received real or sham tDCS completed a 10-point VAS of tDCS related discomfort. The mean discomfort rating was used to assess tDCS-related discomfort for the real tDCS+ABMT group. A group average rating ≤4 (i.e., mild discomfort) would indicate that the intervention was well tolerated. The frequency and severity of side-effects were also reported.

The primary clinical outcome was the change in monthly episodes of objective binge eating from baseline (T0) to follow-up (T2), as measured by the Eating Disorders Examination Questionnaire [EDE-Q, Fairburn and Beglin (2008)]. Episodes of objective binge eating in the previous month were drawn from items 13 and 14 of the

EDE-Q. Item 13 asks, “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?” and item 14 follows with: “On how many of these times did you have a sense of losing control over your eating?”. Responses to item 14 were used to assess the number of episodes of objective binge eating in the previous 4 weeks. We did not pre-specify the minimum effect size required for progression to a larger trial, but the effect size observed will inform sample size selection. In addition. secondary outcomes assessed change in ED symptomatology, general psychopathology, craving for food, difficulties with emotion regulation and quality of life from baseline to post-treatment (T1) and follow-up (T2).

5.3.5 Outcome measures

ED symptoms were assessed using the Eating Disorders Examination Questionnaire (EDE-Q; Fairburn & Beglin, 2008). Episodes of objective binge eating were taken from the EDE-Q item about binge eating in the previous 28 days. Self-reported weight and height were also used to calculate body mass index at each timepoint.

General psychopathology was assessed using the Depression, Anxiety and Stress Scale (21 item version; Lovibond & Lovibond, 1996). Craving for food was examined using the Food Craving Questionnaire (trait version; Cepeda-Benito et al., 2000). Emotion dysregulation was assessed using the Difficulties in Emotion Regulation Scale (DERS; Bjureberg et al., 2016) and the impact of the ED on quality of life was assessed using the Clinical Impairment Assessment (CIA; Bohn & Fairburn, 2008). For all measures, higher scores indicated greater levels of symptom severity or impairment. See Appendix H for copies of outcome measures.

5.3.6 Procedure

After potential participants had provided written informed consent, they were screened against inclusion/exclusion criteria over the phone. At screening, BED diagnosis was confirmed with the Eating Disorders Diagnostic Scale (Stice, et al., 2000). Physical and psychiatric comorbidities, current medications, and tDCS safety were assessed using a general health questionnaire developed for the purpose of this study. Eligible participants then completed the baseline (T0) assessment after which they were randomised to one of four groups: (1) ABMT + real tDCS, (2) ABMT + sham tDCS, (3) ABMT only, or (4) WL. Intervention groups then completed 10

sessions of their allocated treatment, up to 5 sessions/week, across 2-3 weeks. During this time, the WL group received no experimental treatment. All participants then completed the post-treatment assessment (T1) after the 10th (final) session of treatment or after 2-weeks of waiting (WL group). Six weeks later (i.e., 6 weeks after completing treatment or after 8-weeks of waiting) participants completed the final (T2) follow-up assessment. Following this, WL participants were invited to commence ABMT. At each assessment participants completed questionnaire measures (as described above) and neurocognitive tasks (as described in Flynn et al (2022) and reported in Chapter 6).

5.3.7 Data analysis

Descriptive statistics were used to assess recruitment and retention rates, intervention adherence, and the quality and completeness of the data.

First, to examine the effect of treatment on the primary outcome, objective binge eating episodes at follow-up, we examined effect sizes for change scores (Hedge's g) from baseline to post-treatment and follow-up in the first instance. Hedge's *g* is a measure of effect size which provides more stringent control for inflation in studies using a small sample size (e.g., $n < 20$). The effect size expresses the difference of the means in units of the pooled standard deviation. Cohen (1977) proposed a "rule of thumb" for interpreting Hedge's *g:* effect sizes ≤ 0.2 are small, ≤ 0.5 are moderate, ≤ 0.8 are large.

Second, to examine the effect of treatment on objective binge episodes, a Generalised Linear Model was used where the dependent variable (number of objective binge eating episodes, EDE-Q) was modelled by a negative binomial distribution with a log link. The design was one repeated factor (time) with 2 levels (baseline and follow-up) and one between-subjects factor (study group) with 4 levels (real tDCS+ABMT, sham tDCS+ABMT, ABMT only, and WL), and one co-variate (BMI at baseline). Importantly, in Flynn et al. (2022), it was proposed that we would explore the effect of treatment on objective binge episodes using Poisson regression for count data however, given that there was overdispersion in the model (i.e., the variance of binge eating episodes was larger than what would be expected of a true Poisson distribution), negative binomial regression was used (Hausman et al., 1984). Given insufficient power, p-values are reported for exploratory purposes only.

Third, to examine the effect of treatment on secondary outcomes we examined effect sizes for change scores from baseline to post-treatment and follow-up. Analyses were completed in the intent-to-treat population, which is defined by including all patients randomised to an intervention group. Analyses were conducted using RStudio (R: Core Team, 2013) and STATA (StataCorp, 2017).

5.4 Results

5.4.1 Feasibility outcomes

5.4.1.1 Participant flow, attendance, and retention

Figure 5.1 CONSORT diagram of participant flow

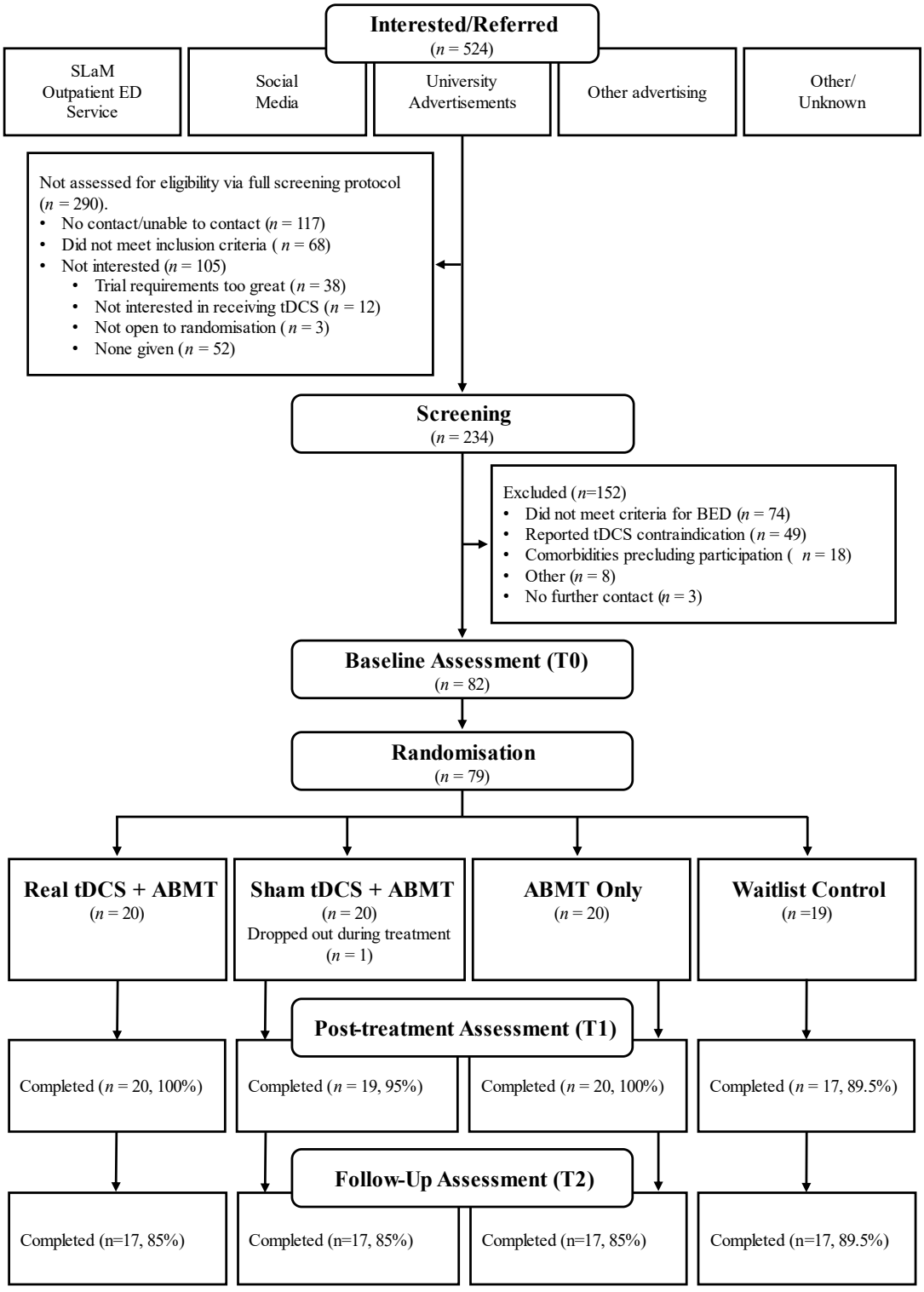


Table 5.1. Baseline characteristics

	Whole Sample (*n* = 82)	Real tDCS+ABMT (*n* = 20)	Sham tDCS+ABMT (*n* = 20)	ABMT Only (*n* = 20)	WL (*n* = 20)
Demographic Details					
Age (mean [SD])	42.18 (9.49)	40.40 (9.83)	40.45 (7.88)	43.70 (10.60)	43.52 (9.85)
Female Sex (n [%])	80 (97.60)	19 (95.0)	19 (95.0)	20 (100.00)	19 (100.00)
Clinical Characteristics					
BMI (mean [SD])	39.96 (7.46)	39.00 (6.79)	39.18 (8.47)	40.48 (8.61)	40.20 (6.58)
History of Bariatric Surgery (n [%])	3 (3.7)	1 (0.05)	1 (0.05)	1 (0.05)	0 (0.00)
EDE-Q Global (mean [SD])	4.04 (0.86)	4.00 (0.80)	3.98 (0.79)	4.20 (0.80)	3.98 (1.11)
EDE-Q Monthly OBEs (mean [SD])	19.63 (9.46)	19.58 (10.20)	18.85 (11.90)	21.05 (8.81)	19.00 (6.65)
DASS-21 Depression (mean [SD])	16.39 (11.04)	18.10 (11.54)	14.30 (10.02)	17.80 (11.66)	15.89 (12.06)
DASS-21 Anxiety (mean [SD])	8.02 (6.69)	7.60 (6.79)	8.20 (8.26)	9.00 (6.73)	7.26 (5.04)
DASS-21 Stress (mean [SD])	17.41 (8.11)	18.70 (10.63)	16.60 (7.37)	18.50 (7.13)	16.63 (7.43)
DASS-21 Total (mean [SD])	41.83 (21.79)	44.40 (25.25)	39.10 (21.75)	45.30 (20.10)	39.79 (21.86)
FCQ-Tr Total (mean [SD])	63.05 (8.25)	63.90 (8.40)	60.45 (7.80)	64.30 (8.66)	62.79 (8.54)
DERS (mean [SD])	32.23 (15.95)	36.40 (18.41)	29.90 (14.89)	32.60 (14.67)	30.00 (16.75)
CIA (mean [SD])	1.53 (0.56)	1.49 (0.59)	1.43 (0.40)	1.65 (0.61)	1.50 (0.64)
Comorbidities					
Depression (n [%])	50 (61.00)	15 (75.00)	11 (55.00)	11 (55.00)	12 (63.20)
Anxiety (n [%])	34 (41.50)	9 (45.00)	9 (45.00)	8 (40.00)	8 (42.11)
Diabetes Mellitus (Type II) (n [%])	13 (15.90)	6 (30.00)	2 (10.00)	3 (15.00)	2 (10.53)
Prediabetes (n [%])	7 (8.50)	1 (0.05)	1 (0.05)	3 (15.00)	1 (0.05)
Hypertension (n [%])	24 (29.30)	5 (25.00)	7 (35.00)	8 (40.00)	2 (10.53)
Hyperlipidaemia (n [%])	15 (18.30)	1 (0.05)	5 (25.00)	6 (30.00)	2 (10.00)
Hypothyroidism (n [%])	13 (15.90)	4 (20.00)	2 (10.00)	3 (15.00)	3 (15.79)
Concurrent Psychological Treatment					
Guided Self Help (n [%])	3 (3.66)	1 (0.05)	1 (0.05)	1 (0.05)	0 (0.00)
Antidepressant Medication (n [%])	41 (50.00)	11 (55.00)	10 (50.00)	9 45.00)	10 (52.63)

Note: No statistically significant difference between-groups at the $p < 0.05$ level. Abbreviations (in alphabetical order): ABMT, attention bias modification training; BMI, body mass index; CIA, Clinical Impairment Assessment; DASS-21, Depression, Anxiety and Stress Scale – 21 items; DERS, Difficulties with Emotion Regulation Scale; EDE-Q; Eating Disorders Examination Questionnaire; FCQ-Tr, Food Craving Questionnaire-Trait reduced version; *n,* number of observations, OBEs, objective binge eating episodes; SD, standard deviation, tDCS, transcranial direct current stimulation; WL, wating list;

Participant flow is illustrated in Figure 5.1. Eighty-two participants completed baseline assessment (T0) before being randomly allocated to one of the four study arms. Prior to randomisation, three participants withdrew from the study. In each case, the participant withdrew within 48 hours of baseline assessment and cited a positive diagnosis of COVID-19 as the reason for withdrawal. Seventy-nine participants were randomised to one of the four study arms: real tDCS+ABMT (n = 20), sham tDCS+ABMT (n = 20), ABMT only (n = 20), and WL (n = 19). During treatment, one participant (sham tDCS+ABMT) tested positive for COVID-19 and stopped treatment after 5 sessions. All other participants completed treatment, with 65% adhering to the optimal treatment protocol (i.e., 10 sessions across 10 consecutive weekdays).

Seventy-six participants completed the post-treatment (T1) assessment, and 68 participants completed the follow-up assessment (T2), giving retention to follow-up rates of 92.7% and 82.9%, respectively. Independent t-tests suggested no significant differences between those who completed post-treatment/follow-up assessments and those who did not, based on age, BMI, ED symptom severity, or DASS-21 total score. As such, missing data were viewed to be missing completely at random and was accordingly managed using case-wise deletion.

5.4.1.2 Participants

Demographics and baseline clinical characteristics are presented in Table 5.1. Additional demographic information is summarised in Appendix A.9.

5.4.1.3 Acceptability

At both post-treatment and follow-up, 100% of participants who received either real or sham tDCS with ABMT declared that they would recommend the intervention to a friend if they were struggling with BED. Similarly, most who received real tDCS, as opposed to sham, indicated that they would continue the treatment if they could (100% at T1, 95% at T2). In contrast, participants who received sham were less likely to endorse continuing treatment, with 74% in favour at post-treatment and 68.4% in favour at follow-up. Among those who received ABMT only, most

indicated that they would recommend treatment to a friend if they were struggling with BED (76% at T1, 72% at T2), but few indicated that they would continue treatment beyond the trial if they had the choice (46% at T1, 23% at T2).

5.4.1.4 tDCS tolerability

On average, participants who received real stimulation reported discomfort levels of 1.2/10 (SD = 1.18) in the first week of treatment, and 2.37/10 in the second week of treatment. In the sham cohort, participants rated discomfort 0.23/10 (SD=0.45) and 0.69/10 (SD=0.2) in weeks 1 and 2 of treatment, respectively. Two participants in the real tDCS group reported mild headache following their first tDCS session. One participant in the sham tDCS group reported mild neck pain after their first session, and two participants reported mild headache after stimulation on one occasion. There were no significant differences between real and sham groups in the number of physical complaints (i.e., headache, neck pain, pain at the site of stimulation) experienced during treatment ($x^2(1) = 0.46$, p = 0.638).

5.4.1.5 Blinding success

Participants did not distinguish real from sham tDCS at a rate better than chance at either post-treatment [48.7%, ($x^2(1) = 1.17$, $p = 0.533$)], or follow-up [41.0, ($x^2(1) = 1.21$, p = 0.323)], and at each time point they expressed little confidence in their choice (post-treatment VAS mean = 4.50, SD = 2.21; follow-up VAS mean = 5.00, SD=2.33).

5.4.2 Clinical outcomes

Between-group effect sizes for change scores to post-treatment (T1) and (T2) are summarised in Table 5.2. Mean scores for clinical outcome measures are presented in Appendix A.10 and change scores are presented in Appendix A.11.

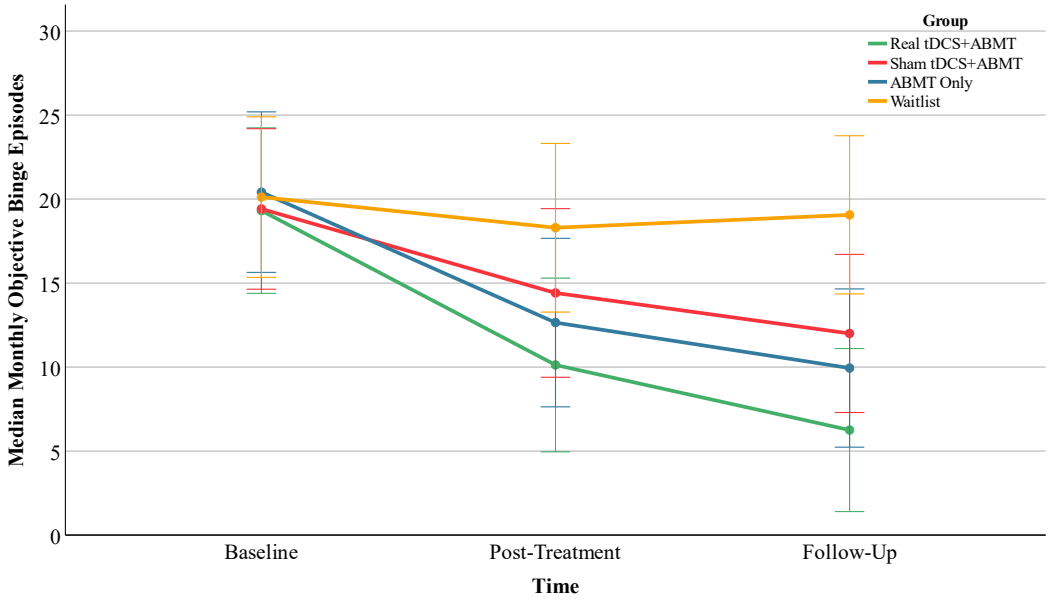
5.4.2.1 Episodes of objective binge eating

All intervention groups reported a reduction in episodes of objective binge eating from baseline to follow-up. Figure 5.2 illustrates the change in number of episodes of objective binge eating reported over time by group. Effect sizes for objective binge eating change to follow-up were large when comparing each intervention group with WL control, and all favoured the intervention group (real tDCS+ABMT: d = -1.3,

95% CI = -2.08, -0.56, sham tDCS+ABMT: d= -1.20, 95% CI = -1.93, -0.46, ABMT only: d = -1.05, 95% CI = -1.77, -0.33). When comparing ABMT with real tDCS, as opposed to sham, a moderate effect size for objective binge eating change which favoured real tDCS+ABMT was observed (d = -0.58, 95% CI = -1.28, 0.12). Similarly, when comparing real tDCS+ABMT with ABMT only, a small effect size which favoured real tDCS+ABMT was reported (d = -0.21, 95% CI = -0.9, 0.47). A small effect size favoured ABMT only when comparing sham tDCS+ABMT with ABMT only (d = 0.32, -0.36, 0.99).

Negative binomial regression indicated that, overall, treatment group was a significant predictor of the number of monthly episodes of objective binge eating reported at follow-up (x^2 = 9.55, df = 3, p < 0.04). Based on this model, the predicted incident rate for objective binge episodes at follow-up was 33% lower in real tDCS+ABMT than in the WL control (exp(β) = 0.33, SE = 0.37, p < 0.01, 95% CI = -0.16, 0.67). There was no difference in the predicted incident rate for objective binge episodes for participants in the sham tDCS+ABMT group (p = 0.192) or the ABMT only group (p = 0.07), relative to WL control.

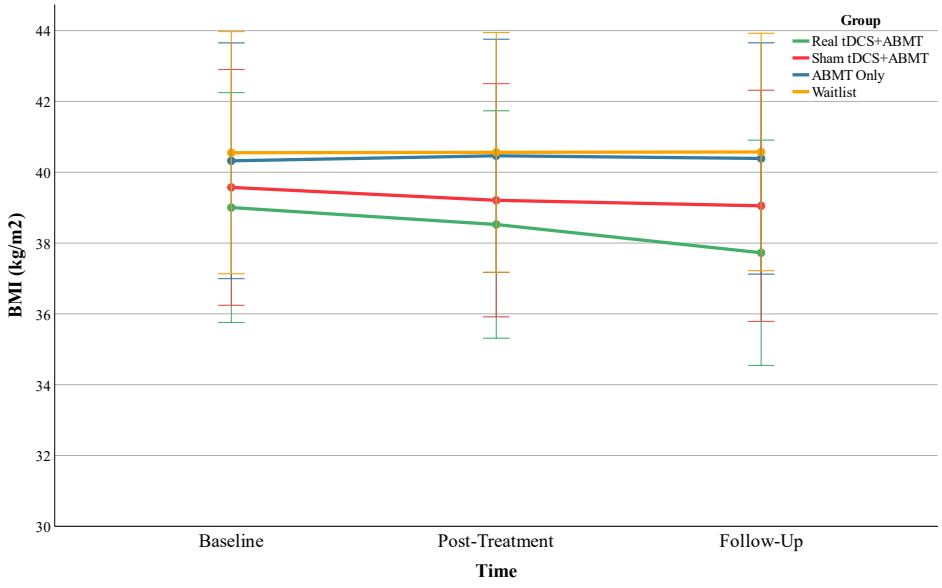
Figure 5.2. Change in monthly episodes of binge eating from baseline to follow-up (95% confidence intervals).



5.4.2.2 BMI

At follow-up, participants who received real tDCS+ABMT reported a mean weight loss equivalent to a 1.28 kg/m^2 reduction in BMI (SD = 0.1.48), and those who received sham tDCS+ABMT reported a mean reduction in BMI of 0.52 kg/m^2 (SD = 0.56). Those who received ABMT only reported minimal change in BMI at either post-treatment (mean change = -0.14 kg/m^2, SD = 0.49) or follow-up (mean change = -0.67 kg/m^2, SD = 0.53). No change in BMI was reported by the WL control group (mean change to follow-up = 0.03 kg/m^2, SD = 0.17). For groups that received ABMT with either real or sham tDCS, relative to WL, effect sizes for change in BMI to follow-up were large and favoured the intervention group (real tDCS+ABMT: d = -1.21, 95% CI = -1.90, -0.51, sham tDCS+ABMT: d = -1.12, 95% CI -1.81, -0.42). Effect sizes for BMI change scores for ABMT with both real and sham tDCS, relative to ABMT only, were large and in favour of the combined real/sham interventions (real tDCS + ABMT: d = -1.20, 95% CI = -1.88, -0.50, sham tDCS+ABMT: d = -0.98, 95% CI = -1.65, -0.30). For ABMT with real tDCS, as opposed to sham, there was a small effect size for BMI change which favoured the real tDCS intervention group (d = -0.20, 95% CI = -0.83, 0.43). Large effect size for BMI change scores favoured the sham tDCS+ABMT intervention, when comparing it to ABMT only (d = -0.98, 95% CI = -1.65, -0.30).

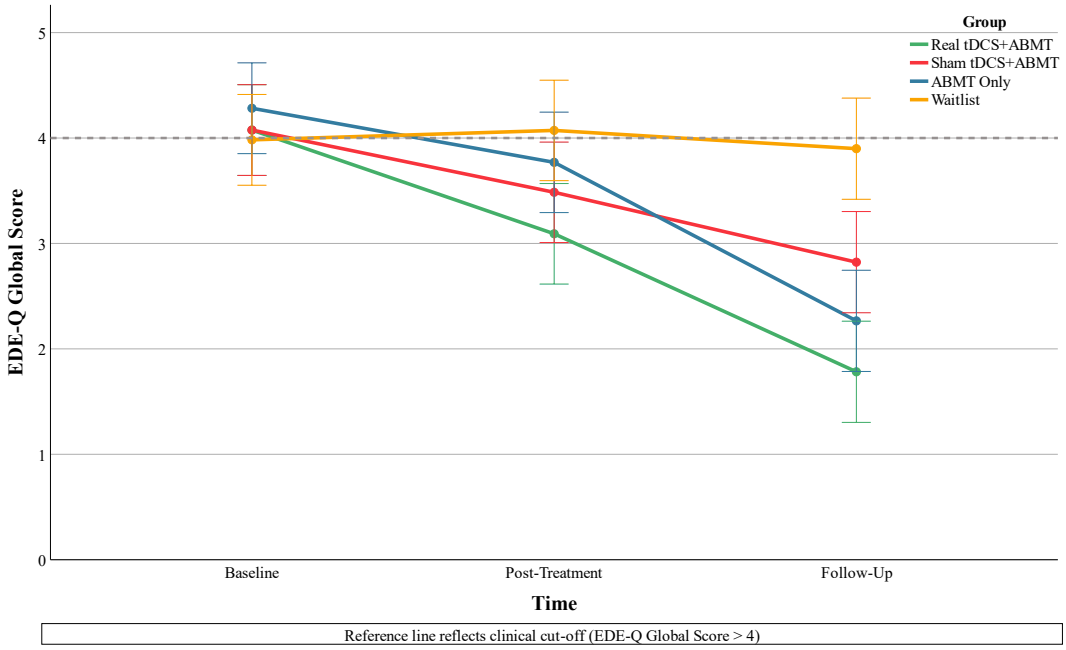
Figure 5.3. Change in BMI from baseline to follow-up (95% confidence intervals).



5.4.2.2.1 Eating disorder psychopathology

Figure 5.4 illustrates the change in ED symptoms from baseline to post-treatment and follow-up. When comparing each intervention group with WL, effect sizes for EDE-Q global change scores to follow-up were large and in favour of the intervention group (real tDCS+ABMT: d= -2.45, 95% CI = -3.34, -1.14, sham tDCS+ABMT: d= -1.62, 95% CI = -2.39, -0.83, ABMT only: d= -2.38, 95% CI = -3.25, -1.48). Similarly, when comparing ABMT with real, as opposed to sham tDCS, effect sizes for change scores to follow-up were large and in favour of the real tDCS+ABMT (d = -1.09, 95% CI = -1.80, -1.36). A small effect size for change scores to follow-up favoured the real tDCS+ABMT group, as opposed to ABMT only (d = -0.27, 95% CI = -0.94, 0.41), and a large effect size favoured ABMT only, when comparing it to sham tDCS+ABMT (*d* = 0.87, 95% CI = 0.16, 1.57).

Figure 5.4. Change in ED symptoms over time (EDE-Q Global Score; 95% confidence intervals)

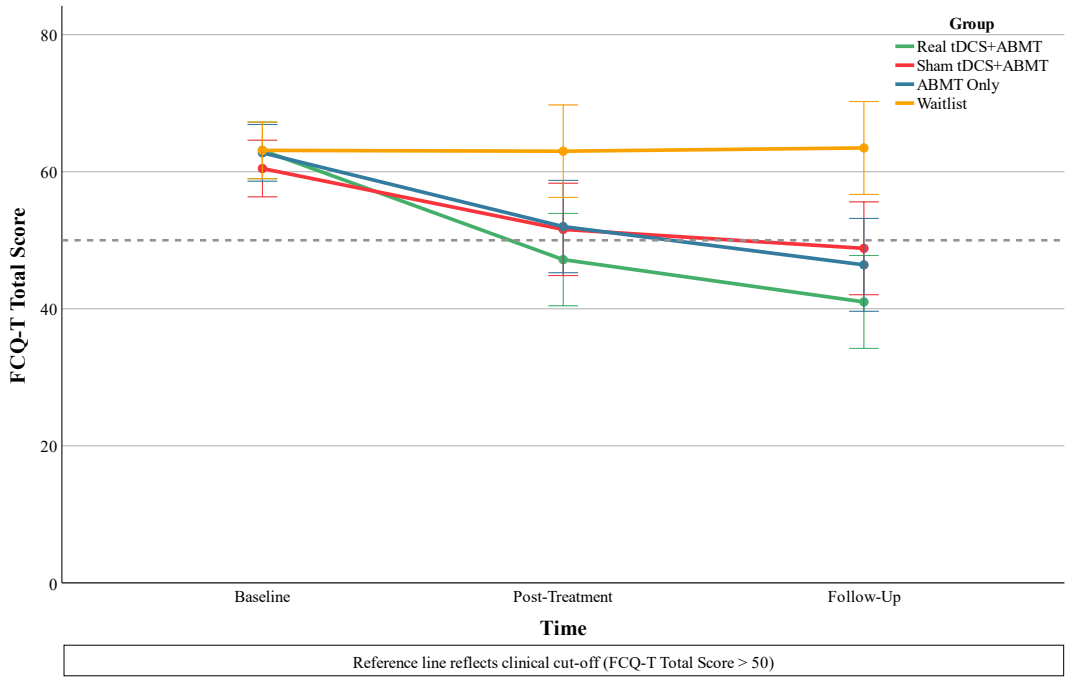


5.4.2.2.2 Craving for food

Trait craving for food, as measured by the FCQ-Tr, was also reduced in each intervention by follow-up, and large effect sizes for change scores relative to WL were observed (real tDCS+ABMT: *d* = -2.06, 95% CI = -2.89, -1.21; sham

tDCS+ABMT: *d* = -0.93, 95% CI = -1.64, -0.22; ABMT only: *d* = -1.26, 95% CI = -2.00, -0.52). Here, small-to-moderate effect sizes for change scores were observed for real tDCS+ABMT relative to ABMT only (*d* = -0.36, 95% CI = -1.03, 0.32) and combined treatment with sham tDCS (*d* = -0.66, 95% CI = -1.35, 0.03), both of which favoured the real tDCS+ABMT group.

Figure 5.5. Change in craving for food (trait) from baseline to follow-up (95% confidence intervals)

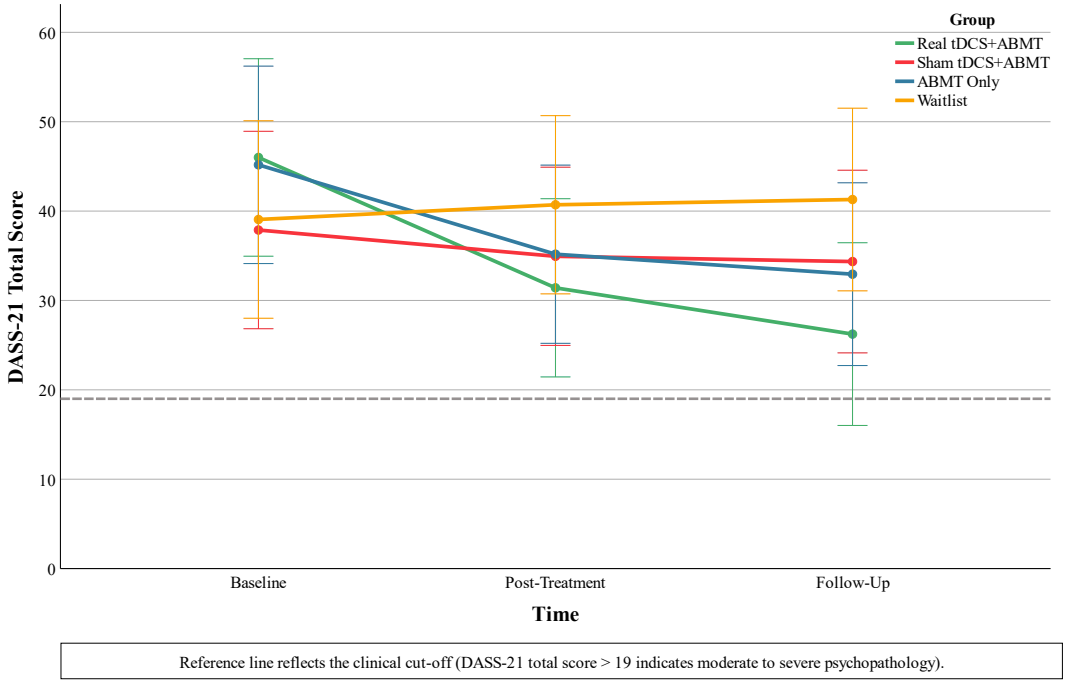


5.4.2.2.3 General psychopathology

Figure 5.6 illustrates the change in total score on the DASS-21 measure of depression, anxiety, and stress from baseline to post-treatment and follow-up. When comparing real tDCS+ABMT to the WL control, effect sizes for DASS-21 total change scores to follow-up were large and favoured the intervention group (*d* = 1.15, 95% CI = -1.87, -0.41). Similarly, effect sizes for DASS-21 total change scores were large for ABMT only (*d* = -1.18, 95% CI = -1.90, -0.44), and moderate for the sham tDCS+ABMT group (*d* =-1.15, 95% CI = -1.09, 0.27), relative to WL control. When comparing real tDCS+ABMT with ABMT only, effect sizes for DASS-21 total change scores were moderate and in favour of the real tDCS+ABMT intervention

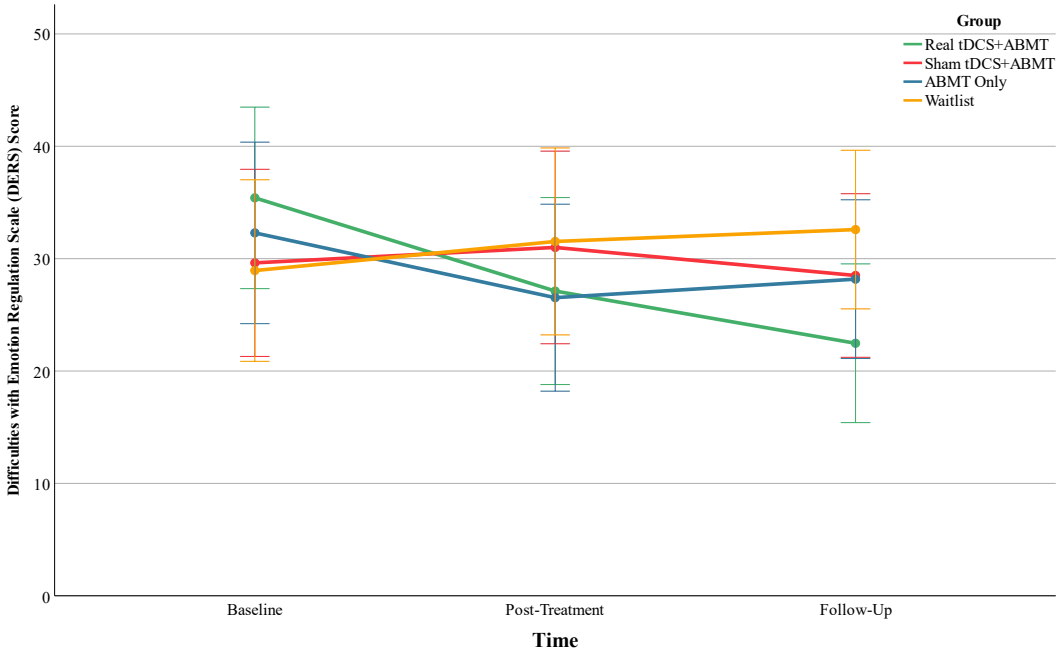
group (*d* = -0.41, 95% CI = -1.09, 0.27). Similarly, large effect sizes for DASS-21 total change scores favoured the real tDCS+ABMT group, as opposed to sham tDCS+ABMT (*d* = -0.80, -1.54, -0.13).

Figure 5.6. Change in general psychopathology over time (DASS-21 Total Score; 95% confidence intervals)



With respect to change in self-reported difficulties with emotion regulation, as measured by the DERS, moderate-to-large effect sizes for change scores from baseline to follow-up favoured the real tDCS+ABMT group, as opposed to WL control (real tDCS+ABMT: *d* = -1.15, 95% CI = -1.87, -0.41), sham tDCS+ABMT (*d* = -0.91, 95% CI = -1.62, -018), and ABMT only (*d* = -0.67, 95% CI = -1.35, 0.03). For sham tDCS+ABMT and ABMT only, effect sizes for DERS change scores to follow-up were moderate and favoured the intervention groups, as opposed to WL (sham tDCS+ABMT: *d* = -0.43, 95% CI = -1.11, 0.27; ABMT only: *d* = -0.68, 95% CI = -1.37, 0.02). Small effect sizes for DERS change scores favoured the sham tDCS+ABMT group, as opposed to ABMT only (*d* = -0.22, -0.47, -0.90).

Figure 5.7. Change in DERS total score from baseline to follow-up (95% confidence intervals)



5.4.2.2.4 Quality of life

Change to quality of life was examined using the CIA. Relative to WL, moderate-to-large effect sizes for change scores favoured intervention groups (real tDCS+ABMT: *d*= -1.46, 95% CI = -2.21, -0.69; sham tDCS+ABMT: *d*= -0.67, 95% CI = -1.36, 0.02; ABMT only: *d*= -0.69, 95% CI = -1.38, 0.01). Similarly, moderate effect sizes favoured the real tDCS+ABMT group, as opposed to ABMT only (*d*= -0.66, 95% CI = -1.35, 0.03) and sham tDCS+ABMT (*d* = 0.77, 95% CI = -1.46, -0.06). No difference in change scores from baseline to follow was observed for sham tDCS+ABMT relative to ABMT only (*d* = 0.03, 95% CI = 0.07, -0.60).

Figure 5.8. Change in CIA total score from baseline to follow-up (95% confidence intervals)

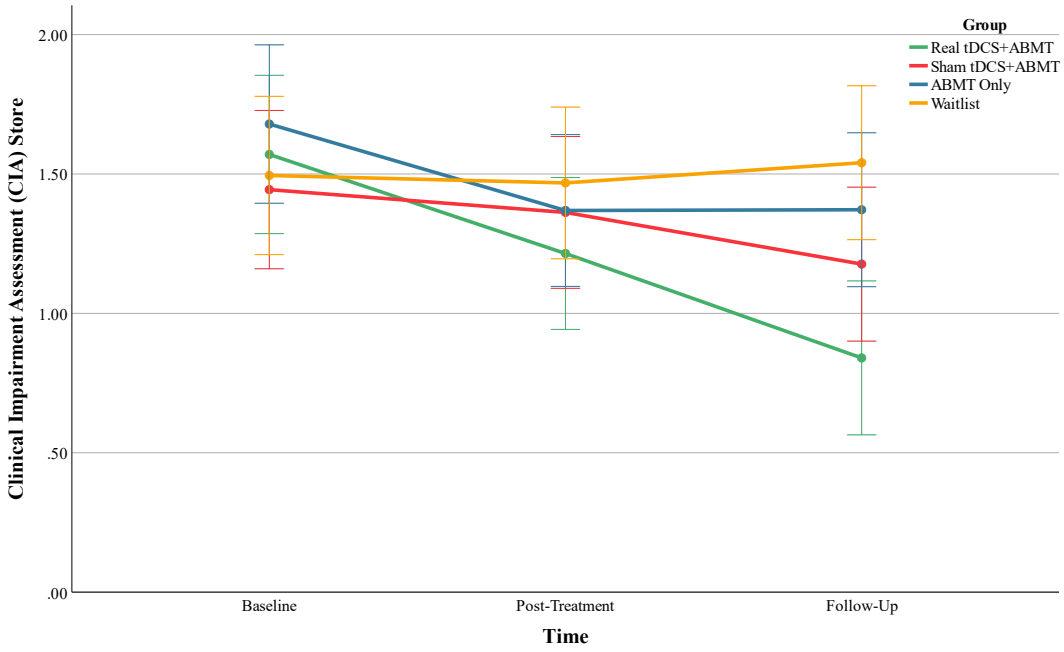


Table 5.2. Between-group effect sizes for change scores* for clinical outcome measures from baseline to post-treatment and follow-up

	Real tDCS+ABMT vs WL			Sham tDCS+ABMT vs WL			ABMT Only vs WL			Real tDCS+ABMT vs ABMT Only			Sham tDCS+ABMT vs ABMT Only			Real tDCS+ABMT vs Sham tDCS+ABMT		
		95% CI			95% CI			95% CI			95% CI			95% CI			95% CI	
	d	Low	High	*d*	Low	High	*d*	Low	High	*d*	Low	High	*d*	Low	High	*d*	Low	High
Change from baseline (T0) to Post-treatment (T1)																		
BMI	-1.11	-1.78	-0.41	-0.89	-1.57	-0.21	0.34	-0.31	0.99	-1.13	-1.80	-0.44	-0.95	-1.61	-0.27	-0.20	-0.83	0.43
EDE-Q Global	-1.92	-2.70	-1.12	-1.79	-2.56	-1.00	-1.18	-1.88	-0.47	-0.63	-1.26	0.01	-0.05	-0.67	0.58	-0.73	-1.37	-0.07
Monthly OBEs	-0.90	-1.58	-0.21	-0.62	-1.29	0.05	-0.98	-1.65	-0.28	0.01	-0.63	0.62	0.35	-0.29	0.98	-0.33	-0.96	0.32
DASS-21 Depression	-0.53	-1.18	0.14	-0.10	-0.75	0.55	-0.53	-1.18	0.14	-0.06	-0.68	0.56	0.47	-0.17	1.10	-0.47	-1.11	0.17
DASS-21 Anxiety	-0.63	-1.29	0.04	-0.35	-1.01	0.31	-0.52	-1.17	0.14	-0.12	-0.74	0.50	0.31	-0.33	0.94	-0.47	-1.11	0.17
DASS-21 Stress	-0.72	-1.38	-0.05	-0.39	-1.05	0.28	-0.89	-1.56	-0.21	-0.08	-0.70	0.54	0.52	-0.12	1.16	-0.46	-1.09	0.18
DASS-21 Total	-0.88	-1.55	-0.20	-0.45	-1.11	0.22	-0.96	-1.64	-0.27	-0.14	-0.75	0.49	0.66	0.01	1.30	-0.63	-1.27	0.01
FCQ-Tr Total	-1.30	-2.01	-0.58	-0.85	-1.53	-0.16	-1.17	-1.86	-0.46	-0.14	-0.76	0.48	0.22	-0.41	0.85	-0.35	-0.98	0.28
DERS	-1.47	-2.19	-0.73	0.11	-0.55	0.76	-0.79	-1.46	-0.12	-0.28	-0.90	0.35	0.84	0.17	1.49	-1.39	-2.09	-0.68
CIA	-0.54	-1.19	0.13	-0.12	-0.78	0.53	-0.85	-1.52	-0.17	0.13	-0.50	0.74	0.58	-0.06	1.22	-0.38	-1.01	0.26
Change from baseline (T0) to Follow-up (T2)																		
BMI	-1.21	-1.90	-0.51	-1.12	-1.81	-0.42	0.12	-0.53	0.76	-1.20	-1.88	-0.51	-0.98	-1.65	-0.30	-0.66	-1.30	-0.01
EDE-Q Global	-2.45	-3.34	-1.54	-1.62	-2.39	-0.83	-2.38	-3.25	-1.48	-0.27	-0.94	0.41	0.87	0.16	1.57	-1.09	-1.80	-0.36
Monthly OBEs	-1.33	-2.08	-0.56	-1.21	-1.93	-0.46	-1.05	-1.77	-0.33	-0.21	-0.90	0.47	0.32	-0.36	0.99	-0.58	-1.28	0.12
DASS-21 Depression	-1.20	-1.92	-0.46	-0.19	-0.87	0.48	-0.62	-1.31	0.07	-0.86	-1.56	-0.15	0.39	-0.29	1.07	-1.06	-1.77	-0.33
DASS-21 Anxiety	-0.67	-1.35	0.03	-0.36	-1.03	0.32	-0.74	-1.43	-0.04	0.11	-0.56	0.78	0.52	-0.17	1.20	-0.42	-1.10	0.26
DASS-21 Stress	-0.77	-1.46	-0.07	-0.39	-1.07	0.29	-1.05	-1.76	-0.32	-0.01	-0.66	0.69	0.67	-0.03	1.35	-0.48	-1.16	0.20
DASS-21 Total	-1.15	-1.87	-0.41	-0.41	-1.09	0.27	-1.18	-1.90	-0.44	-0.41	-1.09	0.27	0.70	0.00	1.38	-0.84	-1.54	-0.13
FCQ-Tr Total	-2.06	-2.89	-1.21	-0.93	-1.64	-0.22	-1.26	-2.00	-0.52	-0.36	-1.03	0.32	0.27	-0.41	0.94	-0.66	-1.35	0.03
DERS	-1.56	-2.32	-0.77	-0.43	-1.11	0.27	-0.68	-1.37	0.02	-0.67	-1.35	0.03	0.22	-0.47	0.90	-0.91	-1.62	-0.18
CIA	-1.46	-2.21	-0.69	-0.67	-1.36	0.02	-0.69	-1.38	0.01	-0.66	-1.35	0.03	0.07	-0.60	0.74	-0.77	-1.46	-0.06

* Post-treatment/follow-up scores minus baseline scores. Abbreviations (in alphabetical order): ABMT, attention bias modification training; BMI, body mass index; CI, confidence interval; CIA, Clinical Impairment Assessment; *d,* effect size estimate using Cohen's *d;* DASS-21, Depression, Anxiety and Stress Scale – 21 items; DERS, Difficulties with Emotion Regulation Scale; EDE-Q; Eating Disorders Examination Questionnaire; FCQ-Tr, Food Craving Questionnaire-Trait reduced version; *n,* number of observations, OBEs, objective binge eating episodes; tDCS, transcranial direct current stimulation; WL, wating list.

5.5 Discussion

5.5.1 Principle findings

The primary objective for this study was to evaluate the feasibility and acceptability of a randomised sham-controlled trial of at-home self-administered tDCS with ABMT in an adult sample with BED. Overall, our findings endorse the pursuit of a future large-scale trial. We were able to randomise 6-7 participants each month for 12 months, which exceeded our minimum criterion, and retention to follow-up rates were high (82.9%). Moreover, treatment session attendance was excellent in all intervention groups: almost all participants completed all 10 treatment sessions within the 3-week maximum timeframe (78/79), and most followed the optimal treatment protocol (i.e., 10 sessions across 10 consecutive weekdays). Of note, stand-alone ABMT was also viewed to be highly acceptable and treatment uptake was extremely high in the WL group: 85% of participants allocated to WL were retained to follow-up and all who completed follow-up assessment took up ABMT and completed at least 7/10 sessions.

These rates for treatment adherence and retention to follow-up compare favourably with those reported in previous related trials. For example, in a recent trial of 6-sessions of tDCS with approach bias modification in BED (n = 65), 71% of participants in the real intervention group and 95% of participants in the sham group completed treatment per protocol (i.e., 2 sessions per week over 3 consecutive weeks), and a retention-to-follow-up rate of 89% was reported (Gordon, *unpublished thesis)*. Similarly, a trial of tDCS with ABMT in adults with alcohol use disorder (n = 98), reported that 86.7% of participants completed all four treatment sessions, although the authors reported significant attrition to 1-year follow-up (den Uyl et al., 2018).

TANDEM treatment adherence and study retention rates were also superior to those observed in trials of ABMT. For example, in their open-label trial of ABMT in BED (n=15), Boutelle et al. (2016) reported that 60% of participants completed treatment (one in-person and two at-home ABMT sessions per week for eight weeks). Relatedly, a recent study comparing ABMT with mindfulness training in adults with obesity reported that although completion rates for lab-based training were high (87% for ABMT and 94% for mindfulness training), adherence to the home practice

protocol was much poorer for ABMT than mindfulness training (Mercado et al., 2023). Indeed, the authors report that, on average, ABMT participants only completed 17/48 of the prescribed at-home training sessions (i.e., 35%), whereas those completing mindfulness training completed 51/48 sessions (i.e., 106%) (Mercado et al., 2023). However, it is worth noting that the prescribed number of ABMT sessions in Mercado et al. (Under Review) was substantially higher than that reported in previous trials. Whilst the effect of cognitive bias modification on symptoms of psychopathology has been shown increase when more sessions are delivered, this effect appears to stabilise after 10 sessions (Beard, 2011). Therefore, 10 sessions may be the optimal dose for ABMT.

Regarding intervention acceptability, our findings indicate that self-administered at-home tDCS was well tolerated by participants; mean discomfort ratings across both weeks suggested that participants only experience mild discomfort during stimulation. Similarly, side effects were reported infrequently (2 occasions in real tDCS and 3 in sham tDCS) and on each occasion they were mild and transient. Participants also viewed the treatment to be highly acceptable, with all indicating that they would recommend tDCS with ABMT to a friend if they were struggling with BED, and nearly all who received real tDCS with ABMT indicating that they would continue the treatment if they could. Indeed, acceptability ratings were higher at both timepoints for the concurrent treatment than for ABMT only.

Participant blinding to tDCS condition was effective, as there were no significant differences between participants' ability to correctly guess whether they had received real or sham stimulation. This aligns with the blinding success reported in previous studies using similar stimulation parameters (e.g., Kekic et al., 2014; Max et al., 2020; Segmond et al., 2019). However, given that the personnel delivering treatment were not blind to treatment allocation, it remains possible (albeit unlikely) that experimenter bias may have influenced our findings. TANDEM was delivered during the coronavirus pandemic; at this time, national lockdowns restricted access to the workplace and limited close contact with colleagues. This led to the pragmatic decision to keep personnel delivering treatment informed of treatment allocation. To reduce risk of bias, future trials should blind the personnel delivering treatment and analysing data to real/sham allocation.

In relation to our primary clinical outcome, all intervention groups reported a reduction in objective binge eating at follow-up, and large effect sizes for change scores favoured intervention groups, as opposed to WL. Although wide overlapping confidence intervals introduce uncertainty, it is possible that real tDCS with ABMT produced the greatest change in objective binge eating at follow-up: the effect size for change in objective binge eating, relative to WL, was largest for the real tDCS with ABMT group, and small-to-moderate effect sizes for change scores, which favoured the real group, were observed when comparing real tDCS with ABMT to sham tDCS with ABMT and ABMT only. Similarly, exploratory analyses suggested that, overall, treatment group was a significant predictor of objective binge episode frequency at follow-up, with objective binge episode count predicted to be 33% lower in the real tDCS with ABMT group than WL. Episodes of objective binge eating were also substantially reduced by ABMT only and ABMT with sham tDCS, although differences between the two interventions were negligible at both time points (i.e., post-treatment and follow-up) and downward trends had plateaued by follow-up. This may suggest a potent therapeutic effect for ABMT in our sample. Indeed, considering the therapeutic effect of ABMT only, evidence for a sham-related placebo effect is limited.

With regard to our secondary clinical outcomes, descriptive statistics showed that real tDCS with ABMT, as opposed to WL, was associated with improvement across several clinical domains. Indeed, they provided tentative evidence to suggest that the real combined intervention may produce superior outcomes from treatment than stand-alone ABMT or ABMT with sham across some domains, namely BMI, mood, craving for food and emotion regulation. First, although ABMT with both real and sham tDCS produced weight loss by follow-up, BMI change was most substantial in the real tDCS+ABMT group (mean BMI reduction = 1.28 kg/m^2). When comparing effect sizes for BMI change scores for intervention groups, relative to WL, the largest effect size for BMI change score was observed for real tDCS with ABMT, and no change in BMI was reported for ABMT only. Similarly, all interventions led to reductions in ED symptoms by follow-up, as measured by the EDE-Q, and effect sizes for change scores, relative to WL, were comparable across groups. This suggests that improvements in ED psychopathology may not be enhanced when ABMT is delivered in combination with real tDCS, although it is worth noting that

EDE-Q global scores were relatively low at baseline (sample mean = 4.04, SD = 0.86). Moreover, participants across all intervention groups reported reduced ED related impairment (as measured by the CIA) at post-treatment, and these effects were maintained through to follow-up.

Second, general psychopathology was also improved across all intervention groups, as demonstrated by large effect sizes for DASS-21 change scores relative to WL. However, change was most pronounced in those participants that received real tDCS with ABMT, particularly when considering the depression subscale only; here, large effect sizes for change scores which favoured real tDCS with ABMT were reported relative to WL, ABMT with sham tDCS, and ABMT only. This suggests that when ABMT and real tDCS are delivered concurrently, a superior antidepressant effect may be achieved. This finding resonates well with those reported in previous clinical trials using tDCS in populations with low mood; namely, that tDCS is associated with pronounced improvement in mood that can endure well beyond the stimulation session, particularly when multiple tDCS sessions are provided (Moffa et al., 2018).

Third, craving for food and difficulties with emotion regulation were both improved by real tDCS with ABMT, relative to WL, and large effect sizes for change scores were reported. By comparison, moderate effect sizes for change scores were reported for sham tDCS+ABMT and ABMT only. This may suggest that superior outcomes from real tDCS with ABMT may be related to tDCS driven changes to DLPFC functioning which, overtime, manifest through improvements in self-regulatory control. Neuroimaging studies have also shown that self-regulation during dietary decision-making requires DLPFC involvement, suggesting that craving may emerge when DLPFC resources are depleted (e.g., Chen, et al., 2018; Wilson, et al, 2021). Similarly, studies in clinical and healthy samples have suggested that the DLPFC plays a central role in the initiation of explicit-controlled forms of emotion regulation (e.g., Siegle, et al., 2007) and, therefore, upregulation of the DLPFC may facilitate emotion regulation.

Overall, our finding that real tDCS with ABMT was associated with substantial, potentially superior, therapeutic effects is consistent with promising findings reported in previous trials using tDCS (Afzali et al., 2021; Burgess et al., 2016; Kekic et al., 2017), cognitive bias modification training (Boutelle et al., 2016; Brockmeyer et al., 2019) or a combination of neurocognitive training and tDCS

(Gordon*, unpublished thesis;* Max et al., 2021) in participants with binge-type EDs. Moreover, the continuation of therapeutic effects to 8 week follow-up (i.e., 6 weeks after end-of treatment) is somewhat unique. Indeed, a previous trial of tDCS with approach bias modification training reported that although episodes of binge eating were reduced by the end of treatment (large effect size), the strength of the effect was reduced by 8-week follow-up, suggesting a possible attenuation of therapeutic effects over time (Gordon, *unpublished thesis)*. However, future large-scale RCTs are needed to substantiate these findings.

5.5.2 Strengths, limitations, and considerations

TANDEM was a feasibility trial, and therefore the primary objective was to assess trial feasibility and intervention acceptability, rather than to evaluate the efficacy of tDCS with ABMT as a treatment. As such, participant numbers were insufficient to evaluate statistically meaningful differences between-groups with confidence. The high rates for recruitment and retention observed during TANDEM indicate that an adequately powered future RCT is feasible. However, consideration should be given to the unique climate during which this trial took place. TANDEM was conducted during the coronavirus pandemic, i.e., a time when people were spending more time at home and interest in virtually delivered psychological and medical care was at an all-time high. These circumstances may have positively influenced people's attitudes about at-home self-administered tDCS with ABMT, as well as their willingness to take part in an RCT.

Additionally, due to the coronavirus pandemic, all components of the TANDEM trial were completed remotely and, as a result, we were able to cast an extremely wide net during recruitment. This likely contributed to the geographic and demographic diversity of individuals in our sample, although male representation was extremely low ($n_{male} = 2$). "The adoption of the fully remote design also required that we sacrifice control over factors that might introduce unwanted variability or bias during outcome assessment. During lab-based assessments, researchers can control a myriad of factors that might influence participant responses (e.g., ambient noise, interruptions, and lighting) and they can make use of instruments which reduce reliance on self-report data (e.g., bioimpedance analysis may be used to assess physical health metrics). In contrast, at-home assessments are vulnerable to interruption and there are few alternatives to self-report data for physical health

metrics. Indeed, this trial relied upon self-report to assess height and weight, and previous studies have demonstrated that adults tend to under-report their own weight, and that the gap between self-reported weight and actual weight increases with obesity (Olfert et al., 2018). Thus, our findings relating to the effect of tDCS with ABMT on BMI should be interpreted with caution. Future trials are encouraged to consider using a hybrid design which allows them to make use of the benefits of lab-based assessment, whilst also retaining the remote treatment model. Where a fully remote study design is required or preferred, we recommend the use of more objective measures for physical health. This may involve completing physical health monitoring with the participant's GP or making use of resources in the community (e.g., specialist scales in pharmacies which provide a receipt summary of physical health metrics).

Reflecting on reasons for ineligibility, our participant flow shows the primary reason for ineligibility was that they did not meet criteria for BED. One possible explanation for this is that the TANDEM trial primarily recruited from the community, as opposed to clinical settings, and relied heavily on social media for advertising. Although this recruitment strategy maximised the number of people who saw study advertisements, it may be that advertisements did not always reach the target audience or that advertisements were not sufficiently clear about the key criteria for taking part. Future trials should consider a more targeted recruitment strategy that includes better connections with services working with people with BED, such as ED outpatient services, general medical practices, ED charities, and eating- and weight-related support groups (e.g., Overeater's Anonymous). Recruitment via these channels could improve the representativeness of the sample by bolstering the number of biological males and gender-diverse individuals included. Future trials could also incorporate a brief online pre-screening questionnaire that addresses simple-to-assess criteria (e.g., BMI > 25kg/m^2, right-handed), thereby reducing the number of interested participants who undergo the full over-the-phone screening that could be quickly identified as ineligible.

Finally, despite reporting frequent episodes of objective binge eating and accompanying distress at baseline (median objective binge episodes= 19.63), mean scores on the EDE-Q at baseline were relatively low (mean EDE-Q Global Score = 4.04). Indeed, this is only marginally higher than the clinical cut-off (Carter et al.,

2001; Mond, et al., 2006). In light of this, the EDE-Q may not be the best instrument for measuring disordered eating behaviour in BED. Although the EDE-Q has strong psychometric properties in ED samples, studies suggest that sensitivity and specificity is poorer for items assessing complex overeating behaviours (i.e., binge eating), as opposed to items about more concrete ED behaviours (e.g., vomiting) (Reas et al., 2006). Fortunately, alternative instruments that have performed well in studies of BED are available. These include the Eating Disorder Examination, which is administered by a trained interviewer, and questionnaire instruments developed for BED specifically (e.g., the Binge Eating Disorder Test of the Binge Eating Scale).

5.5.3 Conclusion

To the best of our knowledge, TANDEM was the first trial to investigate the feasibility of at-home self-administered tDCS in EDs, and the first trial of concurrent tDCS with ABMT in BED. Overall, findings relating to recruitment and retention demonstrate that a future large-scale RCT is feasible, and excellent acceptability ratings indicate that the intervention was well-liked by participants. Preliminary findings relating to clinical efficacy were also promising; all interventions produced improvements in core BED symptoms and related psychopathology, and there was tentative evidence to suggest that real tDCS with ABMT may produce superior outcomes from treatment. However, fully powered RCTs are needed to substantiate these findings.

Chapter 6. Examining the effect of at-home tDCS with attention bias modification training on attention bias towards food: Outcomes from a randomised sham-controlled feasibility trial in binge eating disorder

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Author contribution: The study was conceptualised and designed by the candidate (Michaela Flynn), Professor Ulrike Schmidt and Professor Iain Campbell. The candidate obtained ethical approval from the NHS Research Ethics Committee and the Health Research Authority. The candidate performed all aspects of recruitment, delivery of the trial interventions, data collection, data entry, and data analysis. The candidate drafted the chapter with constructive feedback from her supervisors, Professor Ulrike Schmidt and Professor Iain Campbell.

Abstract

Background: Attention bias (AB) towards high-calorie food is a proposed mechanism in the aetiology and maintenance of binge eating disorder (BED). Using a novel intervention which combined transcranial direct current stimulation (tDCS) with attention bias modification training (ABMT) (Chapter 5), we found that real tDCS with ABMT treatment was associated with therapeutic effects. However, the underlying mechanism of change remains unclear. This chapter aimed to clarify the effect of tDCS with ABMT on AB towards food, and to assess the relationship between AB towards food and clinical outcomes.

Method: This study was a randomised sham-controlled feasibility trial. Eighty-two participants with BED and a body mass index (BMI) of ≥ 25 kg/m^2 were randomly allocated to one of four groups: real tDCS with ABMT, sham tDCS with ABMT, ABMT only, or 6-week waiting list control. Intervention groups received 10 sessions of their allocated treatment over 2-3 weeks. tDCS was administered using a bilateral (anode right/cathode left) montage targeting the dorsolateral prefrontal cortex and 2mA stimulation intensity. Change in AB towards food was assessed at baseline, post-treatment, and 6-week follow-up using the visual probe task with webcam-based eye-tracking.

Results: tDCS with ABMT was associated with a significant reduction in AB for high-calorie food stimuli from baseline to follow-up. Sham tDCS with ABMT and ABMT only also significantly reduce AB towards high-calorie foods between baseline and post-treatment however, differences relative to baseline were non-significant by follow-up. Correlational analyses revealed that change in AB towards food was not significantly correlated with change in clinical symptoms.

Conclusion: tDCS with ABMT was associated with significant reductions in AB towards high-calorie food which were maintained at follow-up however, it remains unclear whether changes in AB towards food were related to therapeutic effects. Future multi-session studies of self-administered tDCS with ABMT are encouraged, however, we recommend future trials reconsider the use of webcam-based eye-tracking, particularly where lab-based alternatives are available.

6.1 Introduction

This chapter presents secondary findings from a randomised controlled feasibility trial of self-administered transcranial direct current stimulation (tDCS) with attention bias modification training (ABMT) in binge eating disorder (BED) (see Chapter 4 for protocol). Specifically, this chapter focuses on the effect of tDCS with ABMT on food-related attention bias (AB). As outlined previously in this thesis, AB towards high-calorie food may contribute to the maintenance of BED. AB occurs during the early stages of information processing and refers to a tendency to preferably detect, orient to, and attend to emotionally or motivationally salient stimuli, as opposed to neutral ones (MacLeod & Mathews, 2012; Mathews & MacLeod, 2005). Recent studies suggest that people with BED tend to have AB towards food cues together with difficulty disengaging from these cues (as measured with eye tracking techniques) (Stojek et al., 2018). Importantly, gaze maintenance on food cues has been shown to contribute to food cravings and to subsequent food consumption in people with overweight and obesity (Hendrikse et al., 2015; Werthmann et al., 2014). Indeed, findings from our cross-sectional study of AB towards food in obesity with and without BED (Chapter 3) demonstrated that craving for food was significantly correlated with AB towards high-calorie food cues, particularly in individuals with BED. Due to the potential role of AB in perpetuating binge eating behaviour, treatment approaches aimed at modifying these biases have been developed (Kemps et al., 2016; Kemps et al., 2014).

It has been proposed that AB towards food may be directly altered using ABMT, a form of cognitive bias modification training, and there is a growing body of research on the effects of ABMT in the context of overeating and disordered eating behaviours. Where these studies have tested the clinical impact of ABMT on overeating behaviours, including binge eating episodes in BED, findings indicate therapeutic potential (Boutelle et al., 2016; Fodor et al., 2017; Schmitz & Svaldi, 2017; Turton et al., 2018). However, effect sizes for change scores are small-to-moderate, and evidence relating to maintenance of therapeutic effects is limited.

Non-invasive brain stimulation (NIBS) techniques, including tDCS, may also be used to alter cognitive processes which perpetuate maladaptive eating behaviour (Brunoni et al., 2019). Indeed, proof-of-concept studies have shown that tDCS

targeting the dorsolateral prefrontal cortex (DLPFC), a cortical target associated with executive functioning and cognitive control, may reduce craving, AB towards food and objective binge eating behaviour in people with BED (Afzali et al., 2021; Max et al., 2021). Findings from single-session studies in both clinical and non-clinical samples have suggested that tDCS may produce greater and longer-lasting neuroplastic effects when delivered alongside an intervention or training that activates disorder-related neural networks (Vanderhasselt & Ottaviani, 2022). Accordingly, randomised controlled trials (RCTs) in patients with psychiatric disorders have reported superior outcomes from treatment when tDCS and neurocognitive training were delivered simultaneously (Heeren et al., 2015; Heeren et al., 2017; Moffa et al., 2018).

In BED specifically, our research group recently examined the effect of concurrent tDCS and approach bias modification training in BED (Gordon, *unpublished thesis*). Here, concurrent tDCS with approach bias modification training was associated with improvement across several clinical domains, and there was tentative evidence to suggest that approach bias modification with real, as opposed to sham, tDCS produced more pronounced changes in clinical symptoms. Additionally, both real and sham tDCS with approach bias modification reduced approach bias towards high-calorie food by follow-up, although there was no evidence to suggest that this reduction was greater in the group that received real tDCS. However, this was a feasibility trial and, therefore, the sample size was small (n = 65). Moreover, due to coronavirus-related lockdowns, several participants were unable to complete the approach-bias component of the follow-up assessment, so power may have been insufficient to detect differences between groups.

In this thesis, we have presented findings from a feasibility randomised sham-controlled trial of self-administered tDCS with ABMT in BED (The TANDEM Trial). As outlined in Chapter 5, findings suggest that the study protocol is feasible, and that the intervention was acceptable and well tolerated by adults with BED. Additionally, changes in clinical symptoms from baseline to follow-up suggested that the real tDCS with ABMT treatment may produce superior therapeutic effects than sham tDCS with ABMT or ABMT only, relative to a waiting list (WL) control. This chapter focuses on the effect of the intervention on AB towards food, and the

relationship between change in AB and change in BED psychopathology.

6.2 Study aims and hypotheses

The primary aim for the TANDEM trial was to assess protocol feasibility and intervention acceptability, and to obtain between-subjects effect size estimates for primary and secondary outcome measures to inform the design of a future large-scale randomised controlled trial (RCT). This chapter aims to:

1. Measure change in AB towards food from baseline to follow-up.
2. Evaluate between-group differences at post-treatment and follow-up.
3. Assess the relationship between change in AB towards food and change in key clinical outcomes (objective binge eating, eating disorder (ED) symptom severity, body mass index (BMI), and general psychopathology).

It was hypothesised that:

1. AB towards food would be significantly reduced from baseline to follow-up in all intervention groups.
2. Reduction in AB towards food would be greatest in the real tDCS with ABMT group, relative to sham tDCS with ABMT and ABMT only.
3. AB towards food would be significantly reduced following tDCS with ABMT relative to waiting list (WL) at post-treatment and follow-up.
4. Change in food related AB would be positively correlated with change in objective binge eating behaviour, trait craving for food, BMI, ED symptom severity and general psychopathology (i.e., reductions in AB towards high-calorie food stimuli would be associated with reduced ED severity and psychopathology).

6.3 Methods

A detailed overview of the study design, participants, intervention, and outcome assessments are provided in the TANDEM protocol paper presented in Chapter 4 (Flynn, et al., 2022), and findings relating to feasibility and acceptability outcomes, and clinical outcomes are described in Chapter 5.

6.3.1 Design, participants, and setting

TANDEM was a single-blind randomised sham-controlled trial with four parallel arms: (1) real tDCS+ABMT, (2) sham tDCS+ABMT, (3) ABMT only, (4) WL. Outcomes were assessed at baseline (T0), post-treatment (T2; immediately after treatment completion or 2-weeks after baseline for WL) and at follow-up (T2; 6-weeks after end-of-treatment or 8-weeks after baseline for WL).

Participants were right-handed community-dwelling adults (≥18 years old) who met criteria for overweight or obesity (BMI ≥ 25 kg/m^2) and met criteria for DSM-5 BED diagnosis. To ensure participants were able to complete treatment and research-related activities, they were also required to have normal or corrected-to-normal vision and access to a laptop or desktop computer with a webcam. Main exclusion criteria were contraindications to tDCS (e.g., history of seizures or migraines).

Potential participants first provided written informed consent, then they were screened over the phone to determine eligibility. Eligible participants were invited to complete the baseline assessment after which they were randomly allocated to one of the four study arms. Participants took part in TANDEM remotely, using a personal laptop or desktop computer with a webcam (i.e., all treatment and research activities were completed from home with researcher support provided via video-call).

6.3.2 Intervention

See Chapter 4 (Section 4.3.6) for a detailed description of the intervention.

6.3.3 Outcome measures

A full list of outcome measures is provided in Chapter 4 (section 4.3.9). However, outcome measures and tasks relevant to this chapter are briefly described here.

Questionnaire Measures

ED symptoms were assessed using the Eating Disorder Examination Questionnaire (EDE-Q; Fairburn & Beglin, 2008). Episodes of objective binge eating were taken from the EDE-Q item about binge eating in the previous 28 days. Self-reported weight and height were used to calculate BMI at each timepoint. General psychopathology was assessed using the Depression, Anxiety and Stress Scale (21 item version, DASS-21; Lovibond & Lovibond, 1996). Craving for food was examined using the Food Craving Questionnaire (trait version; Cepeda-Benito et al., 2000). For all measures, higher scores indicated greater symptom severity or impairment.

Visual Probe Task

The visual probe (VP) task (MacLeod et al., 1986) was used to assess visuo-spatial AB for food cues. Each trial began with a fixation cross presented for 100ms. This was followed by image pairs (one food image and one non-food image) that were presented simultaneously on both sides of a computer screen (3000ms). Immediately after the pictures disappeared, a probe appeared in the location of one of the stimuli (i.e., on the left or right side of the screen). Participants were instructed to press the left or right arrow key according to the location of the probe. The task consisted of two blocks of 60 trials (120 trials total). One block paired non-food pictures with high-calorie food pictures, whereas the other block paired non-food pictures with low-calorie food pictures. The order of the blocks was randomised between participants, and image presentation was randomised within each block. The position of the food, as opposed to non-food pictures, and the position of the probe on the screen was counterbalanced within blocks to ensure food and non-food images appeared equally often on the left and right sides of the screen.

Behavioural AB scores were calculated separately for each participant by subtracting mean reaction time (RT) for responses to valid trials in which the probe was concealed by a food-related image (congruent trial) from those in which the target was concealed by a neutral image (incongruent trial). Mean AB score for food, as well as the mean AB score for high- and low-calorie trial types, was calculated for each participant.

Eye movements were recorded using the participant's webcam to directly measure visual attention towards food and non-food stimuli. Dwell bias was calculated by subtracting the total time spent attending to the non-food stimulus (ms) from the time spent attending to the food stimulus (ms) during each trial. Mean dwell bias for food, as well as the mean dwell bias for high-calorie and low-calorie trial types, was calculated for each participant.

6.3.4 Procedure

After potential participants had provided written informed consent, they were screened against inclusion/exclusion criteria over the phone. At screening, BED diagnosis was confirmed using the Eating Disorders Diagnostic Scale (Stice, et al., 2000). Physical and psychiatric comorbidities, current medications, and tDCS safety were assessed using a general health questionnaire developed for the purpose of this study. Eligible participants then completed the baseline (T0) assessment after which they were randomised to one of four groups: (1) real tDCS+ABMT, (2) sham tDCS+ABMT, (3) ABMT only, or (4) WL. Intervention groups then completed 10 sessions of their allocated treatment, up to 5 sessions/week, across 2-3 weeks. During this time, the WL group received no experimental treatment. All participants then completed the post-treatment assessment (T1) after the 10th (final) session of treatment or after 2-weeks of waiting (WL group). Six weeks later (i.e., 6 weeks after completing treatment or after 8-weeks of waiting) participants completed the final (T2) follow-up assessment. Following this, WL participants were invited to commence ABMT. At each assessment participants completed questionnaire measures online using Qualtrics™ and neurocognitive tasks using Gorilla™. Participants completed a range of neurocognitive tasks (See Chapter 4). Here, we focus on the visual probe task, which was the first task in the neurocognitive battery for all participants.

6.3.5 Data Preparation

As outlined in the study protocol (Chapter 4), analyses were completed in the intention-to-treat population (i.e., all participants with baseline assessment data). Due to technical difficulties with webcam eye-tracking calibration (>5 unsuccessful 9-point-calibration/validation attempts), 31.6% of study participants were unable to complete the visual probe task at baseline (real tDCS+ABMT: n = 5, sham

tDCS+ABMT: n = 6, ABMT only: n = 6, WL: n = 8). As such, the final intention-to-treat sample included 54 participants (real tDCS+ABMT: n = 15, sham tDCS+ABMT: n = 14, ABMT only: n = 14, WL: n = 11). Independent t-tests suggested that there were no differences between those who did and did not complete the visual probe task at baseline based on age, BMI, or ED symptom severity. However, it is noteworthy that among those who did not complete the task (because of calibration/validation failures) most wore glasses (21/25 participants).

Data were missing from 2 participants at post-treatment (one from each of the intervention groups) and 1 participant at follow-up. Independent t-tests showed that there were no differences between completers and non-completers based on the age, BMI, ED symptom severity, or DASS-21 total score. As such, missing data were viewed to be missing completely at random and were managed using case-wise deletion.

For the visual probe task, trials were considered invalid if the response was incorrect or the RT was < 200ms or > 2000ms (Bradley et al., 2003). Baseline eye movement data were excluded for two participants (one from the real tDCS+ABMT only group and one from ABMT only group) as output indicated that calibration was lost during task administration. As such, eye movement data from the remaining 52 participants were included in the data analysis. All eye-movement data from post-treatment and follow-up timepoints was retained.

6.3.6 Data Analysis

Change in AB from baseline to follow-up was assessed using mixed model analysis of variance (ANOVA) with one between-subjects factor (group: real tDCS+ABMT, sham tDCS+ABMT, ABMT only, or WL), one within-subjects factor (time: baseline, post-treatment, and follow-up) and one covariate (Baseline BMI). Planned between-groups contrasts (independent t-tests) assessed differences between intervention groups and WL at both the post-treatment and follow-up timepoints. Planned within-groups contrasts (paired t-tests) assessed change from baseline to post-treatment, and baseline to follow-up for each group. Bonferroni corrections for multiple comparisons were applied for between-groups ($p < .05/3 = .017$) and within-groups ($p < .05/4 = .0125$) comparisons. Analyses were completed separately for both

indices of AB (i.e., AB scores and dwell bias scores). Analyses first examined AB towards food stimuli in general, then AB for high-calorie food stimuli, and finally AB for low-calorie food stimuli.

Bivariate correlations (Pearson's correlation) were used to explore the relationship between AB towards high-calorie food at follow-up and change scores to follow-up for a) objective binge eating, b) trait craving for food, c) BMI, and d) general psychopathology (DASS-21 total score). Correlations were significant at $p < 0.05$.

Table 6.1. Mean attention bias scores (ms) and standard deviations by group over time.

	Real tDCS+ABMT (n = 15)			Sham tDCS+ABMT (n = 14)			ABMT Only (n =14)			WL (n = 11)		
	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3
Behavioural Indices of Attention Bias												
AB score	19.19 (32.03)	-3.86 (31.36)	-15.56 (16.95)	15.11 (20.89)	-2.18 (11.08)	4.74 (23.22)	16.65 (21.61)	7.23 (29.40)	8.93 (36.60)	12.36 (28.24)	14.68 (27.27)	15.61 (26.61)
AB score (HC)	18.67 (35.83)	-19.68 (43.04)	-39.52 (41.35)	14.13 (29.49)	-12.15 (17.99)	-2.82 (33.59)	15.72 (40.03)	1.28 (54.84)	-4.34 (47.96)	18.32 (30.78)	21.77 (46.47)	19.91 (41.67)
AB score (LC)	15.73 (42.86)	12.29 (34.32)	21.50 (28.71)	13.92 (21.34)	3.43 (29.31)	11.28 (37.68)	15.58 (35.17)	12.40 (40.82)	16.39 (33.91)	8.62 (29.87)	6.12 (31.21)	9.18 (30.60)
Eye-Tracking Indices of Attention Bias												
Dwell bias score	102.32 (49.29)	5.15 (159.58)	-39.55 (96.17)	139.02 (96.10)	-18.96 (71.81)	52.62 (172.99)	181.12 (151.42)	-3.58 (127.11)	10.52 (122.38)	143.66 (100.98)	135.80 (107.25)	114.18 (212.08)
Dwell bias score (HC)	149.11 (65.84)	-141.54 (263.58)	-123.48 (91.01)	195.00 (127.98)	-32.71 (102.38)	38.63 (228.05)	223.45 (129.01)	11.63 (164.28)	39.87 (157.36)	205.98 (205.98)	194.32 (187.35)	175.41 (272.97)
Dwell bias score (LC)	51.51 (84.06)	110.32 (187.18)	71.90 (114.16)	82.82 (122.14)	33.56 (66.81)	114.95 (329.45)	85.64 (134.24)	-3.65 (114.97)	49.61 (89.63)	77.53 (118.79)	62.98 (118.72)	67.89 (180.39)

Abbreviations (in alphabetical order): ABMT, attention bias modification training; HC, high-calorie; LC, low-calorie; ms, milliseconds; tDCS, transcranial direct current stimulation; WL, waiting list.

6.4 Results

Means and standard deviations (SDs) for AB scores are presented in Table 6.1. Mean change scores for clinical outcome measures are reported in Appendix A.11. RTs for congruent and incongruent trials on the visual probe task and total fixation times for food and non-food items at baseline, post-treatment, and follow-up (means and SDs) can be viewed at Appendix A.12.

6.4.1 Behavioural outcomes

Regarding overall AB towards food, results from a mixed models ANOVA with one between-subjects factor (group) and one within-subjects factor (time), controlling for baseline BMI, revealed no significant main effect for group (p = .167, η_p^2 = .097) or time (p = .471; η_p^2 = .015). However, a trend-level group by time interaction was observed (F(6, 98) = 2.731, p = 0.054, η_p^2 = .143) (Figure 6.1). Planned between-group contrasts with Bonferroni correction (p < 0.017) revealed no significant differences between groups at post-treatment, however, a trend-level difference between real tDCS+ABMT and WL emerged at follow-up, with lower AB towards food in the real tDCS+ABMT group than the WL group (mean difference = -31.174, 95% CI = -66.34, 3.99, p = .029, Hedge's g = -1.449). No other between-group differences were significant.

Figure 6.1. Bar chart summary of mean AB score for food stimuli over time by group controlling for baseline BMI

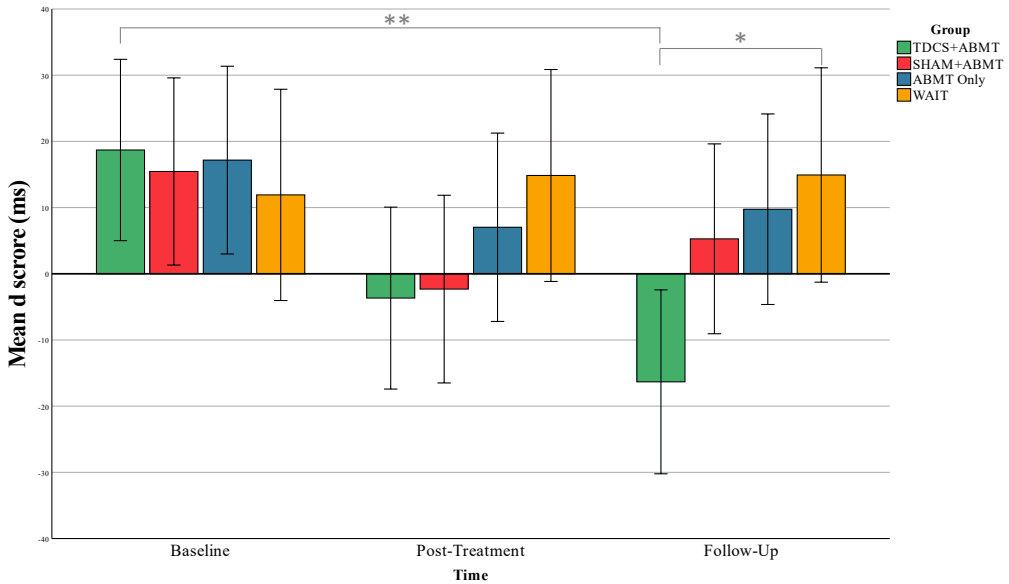

Figure legend: ** Significant after Bonferroni correction. * Significant at p < 0.05 but does not survive Bonferroni correction. Error bars show 95% confidence interval.

Planned within-group contrasts with Bonferroni correction ($p < .0125$) revealed a significant reduction in AB towards food in the real tDCS+ABMT group from baseline to follow up (mean difference = -34.75, 95% CI = -58.14, -11.92, $p < 0.001$, Hedge's g = -1.396) but not post-treatment ($p = 0.058$, Hedge's g = -.0727). No within-group differences over time were observed for the sham tDCS+ABMT, ABMT only or WL groups, and effect sizes were small.

When considering high-calorie food trials only, results from a 4x3 mixed models ANOVA which controlled for baseline BMI revealed a significant main effect for group ($F(3, 49) = 2.875$, $p < 0.05$, $\eta_p^2 = .150$) and a significant group by time interaction ($F(6, 98) = 2.163$, $p < 0.05$, $\eta_p^2 = .118$). No significant main effect for time was found ($p = .914$, $\eta_p^2 = .002$) (Figure 6.2). Planned between-group contrasts with Bonferroni correction ($p < 0.017$) revealed no significant differences between groups at baseline or post-treatment. By follow-up, AB for high-calorie food stimuli was significantly lower in the real tDCS+ABMT group than the WL group (mean difference = -59.42, 95% CI = -105.125, -13.77, $p < 0.005$, Hedge's g = -1.432). No other between-group differences were significant, and effect sizes were small.

Figure 6.2. Bar chart summary of mean AB score for high-calorie food stimuli over time by group controlling for baseline BMI.

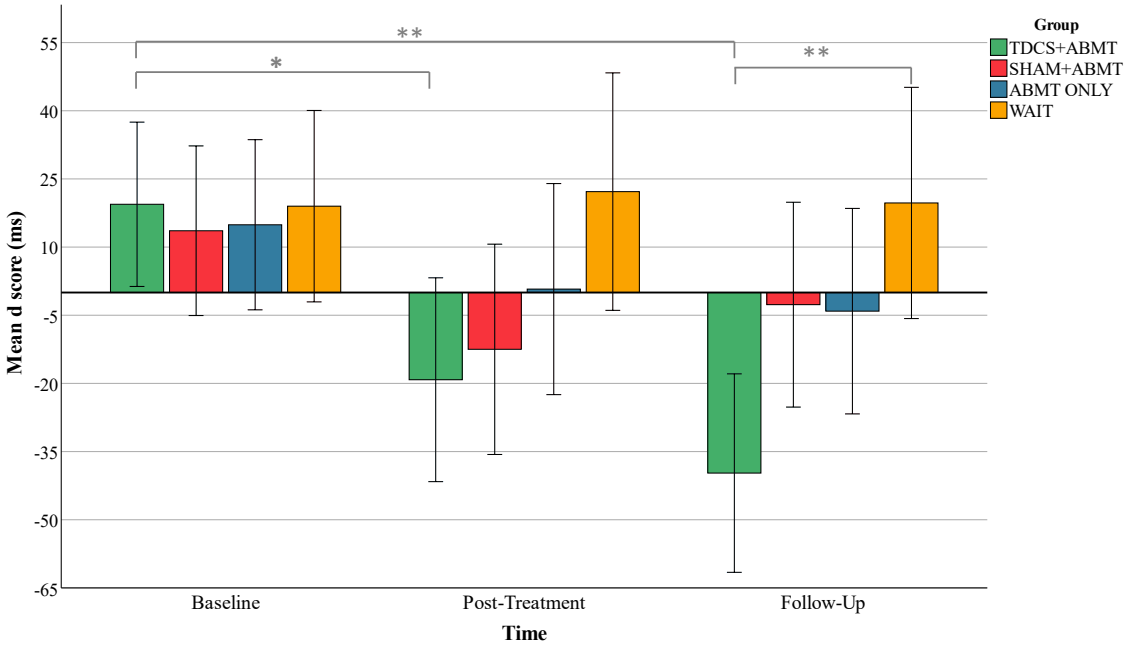

Figure legend: **Significant after Bonferroni correction.* *Significant at* $p < 0.05$ but does not survive Bonferroni correction. Error bars show 95% confidence interval.

Within group contrasts with Bonferroni correction ($p < 0.0125$) revealed a trend level reduction in AB towards high-calorie food in the real tDCS+ABMT group from baseline to post-treatment (mean difference = -38.61, 95% CI = -71.88, -5.340, $p = .018$, Hedge's $g = -.968$). This reduction in AB towards high-calorie food became significant at follow-up compared to baseline (mean difference = -59.15, 95% CI = -92.90, -25.41, $p < 0.001$. Hedge's $g = -1.504$). No other significant within-group differences were observed, and associated effect sizes were small.

When considering low-calorie food trials only, results from a 4 x 3 mixed models ANOVA which controlled for baseline BMI revealed no significant main effect for group ($p = .760$ $\eta_p^2 = .023$) or time ($p = .315$, $\eta_p^2 = .023$), and no significant group by time interaction ($p = .994$, $\eta_p^2 = .007$). See Appendix A.13 for a bar chart summary of mean AB scores for low-calorie food trials by group at each assessment timepoint.

6.4.2 Eye-Tracking outcomes

Regarding overall dwell bias towards food, results from a mixed models ANOVA with one between-subjects factor (group) and one within-subjects factor (time), controlling for baseline BMI, revealed a significant main effect for group ($F(3, 50) = 4.523$, $p < 0.005$, $\eta_p^2 = .213$) but not time ($p = .218$, $\eta_p^2 = .031$), and no-significant group by time interaction ($p = .147$, $\eta_p^2 = .091$) (Figure 6.3). Given the significant main effect for group, we proceeded with planned contrasts comparing intervention groups to WL at post-treatment and follow-up timepoints. Contrasts at post-treatment revealed that, relative to WL, dwell bias towards food was lower in the real tDCS+ABMT group (mean difference = -130.278, 95% CI = 263.495, 2.940, $p = 0.59$, Hedge's $g = -.961$), the sham tDCS+ABMT group (mean difference = -160.83, 95% CI = -296.86, -24.80, $p < .01$, Hedge's $g = -1.696$), and the ABMT only group (mean difference = -146.83 95% CI = -283.26, -10.391, $p < .05$, Hedge's $g = -1.185$), however, these did not survive Bonferroni correction ($p < .017$). Planned contrasts revealed no significant differences between intervention and WL groups at follow-up.

Visual inspection of the means (Figure 6.3) suggested we should also proceed with planned within-group analyses (paired t-tests) with Bonferroni correction ($p < 0.0125$). These revealed no significant change in dwell bias towards for food in the real tDCS+ABMT group from baseline to post-treatment ($p = 0.72$, Hedge's $g =$

-.823), however, there was a trend toward a reduction in in dwell bias towards food from baseline to follow up (mean difference = -136.84, 95% CI = -263.34, -10.34, $p < .05$, Hedge's g = -1.857). In the sham tDCS+ABMT group, there was a significant reduction in AB for food from baseline to post-treatment (mean difference = -159.48, 95% CI = -263.91, -55.04, $p < 0.001$, Hedge's g = -1.875). However, this reduction was not maintained at follow-up (p = .281, Hedge's g = -.619). In ABMT only, dwell bias towards food significantly reduced from baseline to post-treatment (mean difference = -186.98, 95% CI = -291.78, -82.183, $p < 0.001$, Hedge's g = -1.321) and follow-up (mean difference = -175.98, 95% CI = -306.98, -44.99, $p < 0.005$, Hedge's g = 1.239. Dwell bias for food did not change over time in the WL group (p = 1.00).

Figure 6.3. Bar chart summary of mean dwell bias score for food stimuli over time by group controlling for baseline BMI.

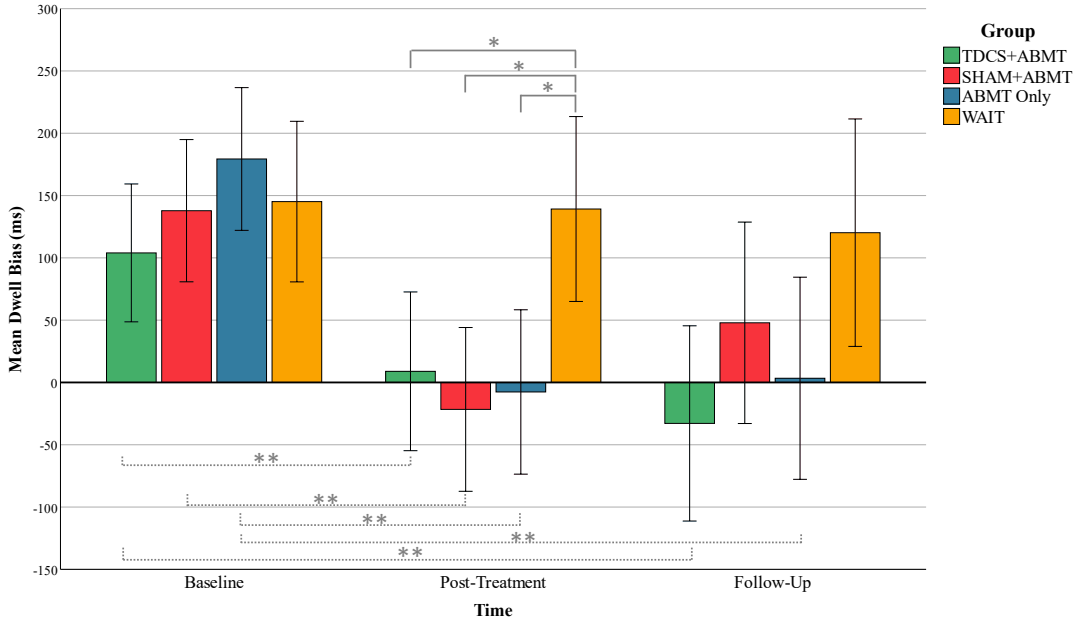

Figure legend: ** Significant after Bonferroni correction. *Significant at p < 0.05 but does not survive Bonferroni correction. Dotted brackets highlight within-group differences. Solid brackets highlight between-group differences. Error bars show 95% confidence interval.

When considering high-calorie food trials only, results from a 4 x 3 mixed models ANOVA controlled for baseline BMI revealed a significant main effect for group ($F(3, 49) = 10.015$, $p < 0.001$, $\eta_p^2 = .380$) but not time ($p = .294$, $\eta_p^2 = .025$), and no significant group by time interaction ($p = .080$, $\eta_p^2 = .107$) (Figure 6.4). Given the large effect size for the interaction, we proceeded with planned contrasts. Between-group contrasts with Bonferroni correction ($p < 0.017$) revealed that there was no

significant difference between groups at baseline (p = .301; η^2= .061). At post-treatment, dwell bias was significantly lower in the real tDCS+ABMT group than in the WL group (mean difference = -335.50, 95% CI = -544.31, -126.69, p < 0.001, Hedge's g = -1.469). Similarly, dwell bias was lower in the sham tDCS+ABMT group than in the WL group (mean difference = -232.88, 95% CI = -446.10, -19.66, p < 0.05, Hedge's g = -1.504), although this difference was not significant after Bonferroni correction. At follow-up, dwell bias was significantly lower in the real tDCS+ABMT group than in the WL group (mean difference = -298.70, 95% CI = -511.031, -86.366, p < .005, Hedge's g = -1.578). No other differences between groups were observed.

Figure 6.4. Bar chart summary of dwell bias score for high-calorie food stimuli over time by groups

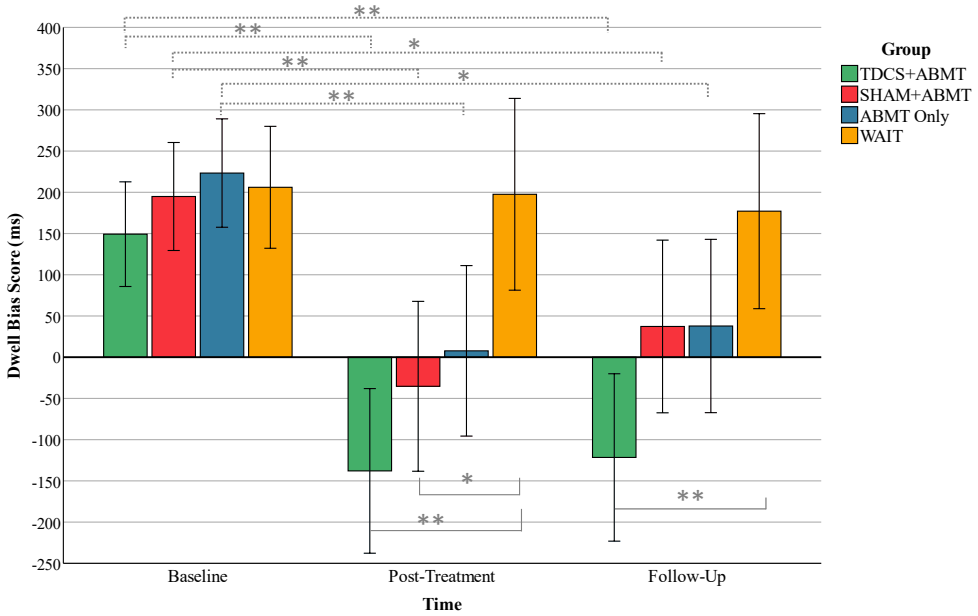

Figure legend: ** Significant after Bonferroni correction. * Significant at p < 0.05 but does not survive Bonferroni correction. Error bars show 95% confidence interval. Dotted bracket denotes within-subjects difference. Solid bracket denotes between subjects difference.

Planned within-group contrasts with Bonferroni correction showed that, in the real tDCS+ABMT group, dwell bias for high-calorie food significantly reduced from baseline to post-treatment (mean difference = -287.12, 95% CI = -432.62, -141.62, p < .001, Hedge's g = -1.513) and follow-up (mean difference = -270.80, 95% CI = -422.62, -118.98, p < .001, Hedge's g = -3.432). In sham tDCS+ABMT, dwell bias towards high-calorie food significantly reduced from baseline to post-treatment (mean difference = -230.20, 95% CI = -380.36, -80.05, p < .001, Hedge's g = -

1.965), but this was non-significant from baseline to follow-up (mean difference = -157.64, 95% CI = -314.31, -.959, $p < 0.05$, Hedge's g = -.995). Similarly, in the ABMT only group, dwell bias significantly reduced from baseline to post-treatment (mean difference = -215.61, 95% CI = -366.28, -64.94, $p < 0.005$, Hedge's g = -1.434), but this was non-significant from baseline to follow-up (mean difference = -185.50, 95% CI = -342.71, -28.29, $p < .05$, Hedge's g = -1.276). Dwell bias for high-calorie food did not change over time in the WL group (p = 1.00).

When considering low-calorie food trials only, results from a 4 x 3 mixed models ANOVA which controlled for baseline BMI revealed no significant main effect for group (p = .629, η_p^2 = .034) or time (p = .186, η_p^2 = .034), and no significant group by time interaction (p = .641, η_p^2 = .042). See Appendix A.14 for a bar chart summary of dwell bias score for low-calorie food stimuli over time by groups.

6.4.3 Correlational Analyses

We did not identify any significant correlation between change in attention bias score and clinical outcomes (monthly episodes of objective binge eating, trait craving for food, ED symptoms severity, BMI, or general psychopathology) at post-treatment or follow-up. Similarly, no significant correlations between dwell bias and clinical outcomes were observed at either timepoint. A full summary of these findings with correlation coefficients and p-values is provided in Appendix A.15.

6.5 Discussion

In line with our hypotheses, our findings indicate that ABMT significantly reduces AB towards high-calorie food stimuli, and that change in AB towards high-calorie food may be most pronounced when ABMT is combined with real tDCS. However, in contrast to our hypothesis, we found no evidence to suggest that reduced AB towards high-calorie food stimuli was associated with improvement in ED symptoms.

When AB was assessed indirectly (i.e., using scores derived from RTs), we observed a significant linear reduction in AB towards food from baseline to follow-up in the real tDCS with ABMT group. This reduction was most pronounced when analyses were limited to trials using high-calorie food items only. Indeed, by follow-up, there was a statistically significant difference between groups, with significantly lower AB for high-calorie food stimuli in the real tDCS with ABMT group than the WL group. In contrast, we found no significant change in food-related AB from baseline to post-treatment or follow-up in either the sham tDCS with ABMT group or the ABMT only group. Similarly, neither group differed from WL control at the post-treatment or follow-up timepoints. However, it is noteworthy that the means for these groups showed a quadratic trend with a convex curve, whereby scores were initially reduced but gradually increased by follow-up. Additionally, although there was no significant difference between groups for AB towards low-calorie food stimuli, and AB towards low-calorie food stimuli did not significantly change over time for any group, there was a visible increase in AB towards low-calorie foods in the real tDCS with ABMT group. Given that participants were trained to "look away" from high-calorie foods and to "look towards" low-calorie foods, this may suggest that bias acquisition was more effective when ABMT was delivered alongside real tDCS.

Similarly, when AB was assessed directly, the real tDCS with ABMT group showed a significant linear reduction from baseline to post-treatment with continued decline at follow-up. As hypothesised, this change was driven by significant reductions in dwell bias for high-calorie food stimuli. Indeed, at post-treatment and follow-up, dwell bias for high-calorie food stimuli was significantly reduced in the real tDCS with ABMT group relative to the WL group. Additionally, the sham tDCS with ABMT group and the ABMT only group showed significantly less dwell bias for high-calorie food stimuli from baseline to post-treatment. Moreover, in the ABMT

only group, this change in dwell bias towards food was maintained at follow-up. Taken together, these findings suggest that ABMT produced significant reductions in dwell bias towards high-calorie food stimuli, and this effect was augmented by simultaneous real tDCS administration.

These findings compare favourably with those reported in a recent study of concurrent tDCS with approach bias modification training (Gordon, *unpublished thesis*). In this feasibility trial, participants received six-sessions of lab-based tDCS during approach bias modification training over three consecutive weeks. Findings suggested that neither real nor sham tDCS with approach bias modification training significantly reduced approach bias for high-calorie food relative to waiting control, and effect sizes for change scores were small. It is plausible that approach bias modification training has poor efficacy in BED, or that a greater number of sessions are needed to achieve meaningful changes in automatic behaviour in the context of food. Indeed, in TANDEM, participants received a greater number of sessions than was used here (ten vs six), and sessions were delivered with greater frequency (every week day vs two visits per week).

It is of note, however, that reductions in AB and dwell bias towards food were not associated with change in clinical symptoms. Our hypothesis that food-related AB and dwell bias would positively correlate with clinical symptoms (i.e., craving for food, objective binge eating episode frequency, BMI, and ED symptom severity) was based on evidence that difficulties in disengaging/elevated gaze maintenance towards high-calorie food stimuli is associated with craving for food and increased binge eating episodes (e.g., Seo & Lee, 2021). One explanation for this finding could be that the magnitude of learning effects throughout ABMT (i.e., indexed by gradual decreases in reaction time) does not predict the magnitude of clinical response in adults with BED. However, only one study has attempted to characterise learning effects during ABMT protocols and examine how it relates to clinical response (Abend et al., 2019). This study was conducted in people with social anxiety disorder and the authors found that ABMT-induced learning gains predicted the magnitude of reduction in self-reported anxiety symptoms, and that this effect was moderated by age. It is vital that future studies evaluate how ABMT-induced learning relates to clinical response, given the important implications this has for the clinical utility of ABMT.

Alternatively, it is possible that other components of attention control are more closely related with clinical outcomes. The visual probe task used here focused on the maintenance of attention (i.e., RTs and eye-tracking for 3000ms trials) however, previous studies of AB in BED have reported AB towards high-calorie food stimuli at the initial orientation stage (i.e., within 200ms) and difficulties disengaging with high-calorie food trials (i.e., after ~500ms). Future trials should incorporate the assessment of early stage attention processes to comprehensively clarify the temporal dynamics of AB towards high-calorie food stimuli in BED and how this relates to clinical symptoms.

A key strength of this study is that it explores the potential mechanisms of change underpinning the therapeutic effects reported in Chapter 5, including reductions in objective binge eating behaviour, improved mood, and weight loss. We strongly encourage future studies to also include mechanistic outcome measures, e.g., neurocognition or biological, to build a comprehensive understanding of the clinical utility of tDCS and ABMT in people with BED. However, several limitations should be considered. First, as a feasibility study the sample size was small, and it was not intended that this study provide definitive findings relating to intervention efficacy. Instead, the aim was to provide proof-of-concept data which may inform the selection of outcome measures for a future large-scale trial and provide effect-size estimates for sample size calculation.

Second, although eye-tracking methods offer a more reliable assessment of AB and provide greater insight into the components of biased attention (Waechter et al., 2014), as discussed in Chapter 3 (section 3.5), webcam-based technologies are not, at present, sufficiently proficient tools for assessing AB. Although evidence from pilot suggests that webcam-based eye-tracking may produce data of comparable quality to lab-based equipment for some eye-tracking paradigms (e.g., Semmellmann & Weigelt, 2018), the consensus in the literature is that these technologies are not yet suitable for paradigms that require detailed spatial resolution of fixations or high spatio-temporal resolution, including those used to assess AB (Anwyl-Irvine et al., 2020). Indeed, in the TANDEM trial, webcam-based eye-tracking was only able to assess dwell bias and, therefore, our understanding of the effect of tDCS with ABMT on AB towards food was limited. Moreover, a substantial number of participants (31.2%) were unable to complete eye-tracker calibration/validation at baseline and

were therefore lost to the intention-to-treat sample. Thus, while we expect that future webcam-based eye-tracking will be a useful tool for assessing attention-related processes, including AB, our findings indicate that this technology is not yet robust enough for use in clinical trials. With this in mind, we recommend that future studies prioritise the use of lab-based eye-tracking equipment when directly assessing AB.

This trial assessed AB using both eye-tracking and response latencies. The reasons for adopting this approach were largely pragmatic, due to the coronavirus-related need to conduct research activities remotely. However, it must be noted that AB indices based on response latencies during the dot-probe task have been shown to have poor internal reliability and test-retest reliability (see Bar-Haim et al., 2007 for review), so continued use of these indices is discouraged.

Third, given the similarities between the visual probe task and ABMT, we recommend that future studies consider using a different outcome measure to assess change in food-related AB. Indeed, recent studies have suggested that the visual probe task, even when paired with eye-tracking, may not be the optimal tool for assessing AB. Rather, free-viewing paradigms have received superior psychometric evaluations in both clinical (e.g., Soleymani, et al., 2020) and non-clinical populations (e.g., Veerapa et al., 2020). Moreover, when paired with eye-tracking with high spatio-temporal resolution (i.e., lab-based eye-tracking), free-viewing paradigms may be used to assess AB across the early, middle, and late stages of attention processing, particularly when presentation duration is long (> 3000ms; Hardman et al., 2021). Functional neuroimaging during food-related attention paradigms may also provide useful insight into the effects of tDCS with ABMT on attention processing. For example, previous studies of attention control in obesity and BED have used functional magnetic resonance imaging (fMRI) during the attention network task with food cues to assess neural activation during the alerting, orienting and re-orienting stages of attention processing (Mercado et al., 2023; Yokum et al., 2011). Future studies which integrate functional neuroimaging with outcome assessment are encouraged, as these will provide insight into the effects of treatment on neural mechanisms underlying attention control and clarify the appropriateness of the DLPFC as a target for tDCS in BED.

Finally, the omission of a sham ABMT group means that we are unable to comment on placebo effects that may be attributable to ABMT. Indeed, meta-analyses of trials

using cognitive bias modification programmes in eating and weight disorders have called for a greater number of trials including a sham training group (Fodor et al., 2017; Turton et al., 2016). As such, RCTs of real vs sham ABMT in BED are also encouraged.

In conclusion, in this first investigation of at-home self-administered tDCS with ABMT we found that real tDCS with ABMT was associated with significant reductions in AB towards high-calorie food which were maintained at follow-up. However, reductions in food-related AB were not related to improvements in clinical outcomes and therefore this warrants further investigation.it remains unclear whether changes in AB towards food were related to therapeutic effects. Future multi-session studies of self-administered tDCS with ABMT which make use of lab-based eye-tracking equipment and free-viewing paradigms are recommended.

Chapter 7. General discussion

Author contributions: The candidate conceptualised and drafted the chapter. Professor Ulrike Schmidt and Professor Iain Campbell reviewed the chapter and provided constructive feedback.

7.1 Thesis Aims

Binge eating disorder (BED) is a common and disabling eating disorder (ED), yet treatment options are limited (Giel, Bulik, et al., 2022; Hilbert et al., 2020). There is a need to develop new treatments for BED, and these may yield superior outcomes if they directly target the mechanisms involved in the development and maintenance of BED. In contemporary neurobiological models, altered cognitive control has been implicated (e.g., Kober & Boswell, 2018), and recent studies have indicated that attention bias (AB) towards high-calorie food may be a potent target for treatment (Stojek et al., 2018). Accordingly, interventions that directly target cognitive control functions, including AB towards food, have been developed. These include attention bias modification training (ABMT), a computerised training programme that aims to reduce the strength of an implicit AB towards high-calorie food cues, and transcranial direct current stimulation (tDCS), a non-invasive brain stimulation (NIBS) technique that uses direct current electric fields to alter cortical excitability and enhance neuroplasticity. Therapeutic effects have been reported following ABMT, however, effect sizes are small (Boutelle et al., 2017; Schmitz & Svaldi, 2017). Similarly, studies have reported that tDCS may reduce craving for food, improve mood and reduce objective binge eating (Afzali et al., 2021; Burgess et al., 2016). Of interest, it is proposed that the effects of tDCS may be enhanced when disorder-related brain regions are activated during stimulation, and that the effects of ABMT may be improved when neuroplasticity is greater. Thus, outcomes from treatment may be superior when tDCS and ABMT are combined.

Accordingly, the work presented in this thesis aimed to:

1. Evaluate the evidence that non-invasive brain stimulation techniques, including tDCS, may achieve influence AB.
2. Clarify the extent to which AB towards food may be a distinct feature of BED, as opposed to a phenotype related to obesity.
3. Assess the feasibility and acceptability of ten-sessions of at-home self-administered tDCS with ABMT in adults with BED.
4. Obtain preliminary evidence relating to the clinical efficacy of at-home tDCS with ABMT, as well as the effect of the intervention on food related AB.

7.2 Main findings

7.2.1 The effects of neuromodulation on AB for emotional stimuli in healthy and clinical populations

The systematic review with meta-analyses presented in Chapter 2 was, to the best of our knowledge, the first to evaluate the effect of NIBS on emotional AB. Our findings indicated that, thus far, there is limited evidence to suggest that NIBS targeting the dorsolateral prefrontal cortex (DLPFC) alters emotional AB, or that the effect of NIBS on AB differs depending on the technique used or the valence of emotional stimuli assessed (i.e., positive or negative). However, as the literature was highly heterogenous, these findings should be viewed with caution. Indeed, it was noteworthy that 80% of studies that used clinical or subclinical samples reported an effect for NIBS on AB for emotional stimuli, and that the pattern of findings in these studies was generally consistent with the theorised effects of NIBS on AB, i.e., that upregulation of the left DLPFC and down regulation of the right DLPFC will reduce AB towards emotional stimuli, whereas down regulation of the left DLPFC and upregulation of the right DLPFC will increase AB towards emotional stimuli. These findings are consistent with the hypothesis that, when applied therapeutically (e.g., to upregulate the left DLPFC and/or down regulate the right DLPFC), NIBS techniques achieve therapeutic effects by improving cognitive control of attention (i.e., reflected in reduced AB).

7.2.2 AB towards food in obesity with and without BED

Chapter 3 presented a cross-sectional study of AB towards food stimuli in fasted adults with obesity with and without BED. As expected, both groups showed an AB towards high-calorie food cues. Interestingly, this bias was not significantly greater in participants with BED, relative to those without BED. Nevertheless, visual inspection of the means suggested a trend for elevated AB towards food in the BED group, which may have become significant in a larger sample. It is possible that differences between individuals obesity with and without BED may also emerge during the early stages of attention processing, rather than during the maintenance stage which was assessed here. Indeed, in previous studies of food-related AB in obesity with and without BED, it has been reported that participants with BED show an early orientation bias towards food and have greater difficulty disengaging with

food stimuli, relative to controls. Additionally, AB towards low-calorie food cues was observed in participants with BED only, suggesting that food, in general, may have high incentive salience in BED.

Regarding appetitive motivation, in contrast to our hypotheses, ratings for current craving, hunger and satiety also did not differ between groups, and AB towards food was not significantly correlated with current hunger or satiety. We did observe the expected positive correlation between AB for high-calorie food cues and craving, and, as expected, this correlation was stronger in the participant group with BED. These findings are mostly consistent with those reported in recent meta-analyses, i.e., that appetitive motivational factors are strongly associated with AB towards high-calorie food cues (Hagan et al., 2020; Hardman et al., 2021). However, it was surprising that current hunger and satiety were unrelated to AB towards food stimuli. This may be related to altered hunger and satiety sensitivity in obesity and BED (Boutelle et al., 2017).

Taken together, findings from this cross sectional study suggest that AB towards high-calorie food is pronounced in fasted individuals with obesity with and without BED. However, it is possible that AB may be distinctive in people with BED. Specifically, BED may be characterised by a particularly strong relationship between craving and AB towards high-calorie food as well as AB towards low-calorie food cues. Future studies that manipulate appetitive motivational factors (e.g., craving and hunger) are needed to characterise the AB phenotype in both populations (i.e., obesity with and without BED).

7.2.3 Feasibility and acceptability of at-home self-administered tDCS with ABMT

Findings from our randomised sham-controlled trial of at-home self-administered tDCS with ABMT suggested that the study protocol was feasible, and that the intervention was viewed to be highly acceptable by participants with BED (Chapter 5). Specifically, recruitment rates exceeded a priori minimum criteria for feasibility (minimum 5 participants per month for 12 months), and retention to follow-up rates were high (82.9%). Similarly, treatment session attendance was excellent in all intervention groups: almost all participants completed all 10 treatment sessions within the 3-week maximum timeframe (78/79), and most followed the optimal treatment protocol (i.e., 10 sessions across 10 consecutive weekdays). Indeed, rates

for treatment adherence and retention to follow up in the TANDEM trial are comparable to those reported in a previous trial of concurrent tDCS with neurocognitive training in BED (i.e., 83.1% completed treatment per protocol and 89% were retained to follow-up assessment; Gordon et al., *unpublished PhD thesis*), and superior to those evaluating stand-alone tDCS treatment (Afzali et al., 2021) or cognitive bias modification in BED (Boutelle et al., 2017; Brockmeyer et al., 2019).

Regarding intervention acceptability, the findings indicate that self-administered at-home tDCS was well tolerated by participants; mean discomfort ratings across both weeks suggested that participants only experienced mild discomfort during stimulation. Similarly, side effects were reported infrequently (2 occasions in real tDCS and 3 in sham tDCS) and on each occasion they were mild and transient. This is consistent with previous studies of tDCS safety and tolerability (Brunoni et al., 2019). Participants also viewed the treatment to be highly acceptable, as demonstrated by high rates of endorsement (i.e., "would recommend to a friend") among those who received the real tDCS with ABMT intervention. Finally, participant blinding to tDCS condition was effective (i.e., participants did not correctly guess real/sham allocation at a rate greater than chance), suggesting that self-administration did not compromise blinding success.

7.2.4 Preliminary evidence for therapeutic effects following self-administered tDCS with ABMT

Preliminary findings from the TANDEM randomised sham-controlled trial of self-administered tDCS with ABMT in BED suggested that all interventions (i.e., real tDCS with ABMT, sham tDCS with ABMT, and ABMT only) had clinical benefit between baseline and follow up, however, real tDCS with ABMT appeared to be associated with superior outcomes from treatment.

With regards to the primary clinical outcome – change in monthly episodes of objective binge eating – all intervention groups reported a reduction in objective binge eating at follow-up, relative to waiting list control (WL) however, effect sizes for change scores were largest for the real tDCS with ABMT group, and small-to-moderate effect sizes for change scores, which favoured the real group, were observed when comparing real tDCS with ABMT to sham tDCS with ABMT and ABMT only. Indeed, exploratory analyses (negative binomial regression) suggested

that treatment group was a significant predictor of objective binge episode frequency at follow-up, with monthly objective binge episode count predicted to be 33% lower in the real tDCS with ABMT group than in the WL group. Accordingly, BMI change was most substantial in the real tDCS+ABMT group (mean BMI reduction = 1.28 units).

General psychopathology was also improved across all intervention groups, however, change was most pronounced in those participants that received real tDCS with ABMT, particularly when considering the depression subscale only. This finding is consistent with those reported in previous clinical trials using tDCS in populations with low mood; namely, that tDCS is associated with pronounced improvement in mood that can endure well beyond the stimulation session, particularly when multiple tDCS sessions are provided (Moffa et al., 2018). Similarly, craving for food and difficulties with emotion regulation were both improved by real tDCS with ABMT, relative to WL, and large effect sizes for change scores were reported. By comparison, moderate effect sizes for change scores were reported for sham tDCS+ABMT and ABMT only. Real tDCS with ABMT superiority may reflect tDCS driven changes to DLPFC functioning which, over time, manifest through improvements in self-regulatory control.

Overall, these findings are consistent with those reported in previous multi-session trials using tDCS (Afzali et al., 2021), cognitive bias modification training (Boutelle et al., 2016; Brockmeyer et al., 2019) or a combination of neurocognitive training and tDCS (Gordon*, unpublished thesis*) in participants with binge-type EDs. However, the continuation of therapeutic effects to follow-up (i.e., 6 weeks after end-of treatment) is somewhat unique. Indeed, a previous trial of tDCS with approach bias modification training reported that although episodes of binge eating were reduced by the end of treatment (large effect size), the strength of the effect was reduced by 8-week follow-up, suggesting a possible attenuation of therapeutic effects over time (Gordon, *unpublished thesis)*.

7.2.5 Change in AB towards food as the mechanism underlying the therapeutic effects associated with concurrent tDCS with ABMT

Findings from the TANDEM trial suggested that, overall, ABMT significantly reduced AB towards high-calorie food stimuli, and that avoidance bias acquisition

may be most pronounced when ABMT is combined with real tDCS. When AB was assessed directly (eye-tracking), we observed a significant linear reduction in AB towards high-calorie food between baseline and follow-up, and at both timepoints, AB towards high-calorie food was significantly reduced relative to WL. In the sham tDCS with ABMT group and the ABMT only group, AB for high-calorie food stimuli was significantly reduced between baseline and post-treatment, albeit to a lesser degree than in the real tDCS with ABMT group. In the ABMT only group, this change in AB was sustained to follow-up. Additionally, although there was no significant difference between groups for AB towards low-calorie food stimuli, and AB towards low-calorie food stimuli did not significantly change over time for any group, there was a visible increase in AB towards low-calorie food stimuli in the real tDCS with ABMT group only. Given that participants were trained to "look away" from high-calorie foods and to "look towards" low-calorie foods, this suggests that bias acquisition was more effective when ABMT was delivered alongside real tDCS.

Correlational analyses revealed no significant relationship between change in AB towards food and change in clinical symptoms. One explanation for this finding could be that the magnitude of learning effects throughout ABMT (i.e., indexed by gradual decreases in reaction time) does not predict the magnitude of clinical response in adults with BED. Alternatively, it may be that AB during the earlier stages of attention control (e.g., orientation bias) may be more closely related to clinical outcomes.

Of interest, the present findings compare favourably with those reported in a recent study of concurrent tDCS with approach bias modification training (Gordon, *unpublished thesis*). In this earlier feasibility trial, participants received six-sessions of lab-based tDCS during approach bias modification training over three consecutive weeks. Findings suggested that neither real nor sham tDCS with approach bias modification training significantly reduced approach bias for high-calorie food cues relative to waiting control, and effect sizes for change scores were small at follow-up. TANDEM differed from the trial by Gordon et al. in a number of ways which may have contributed to divergent findings. First, in In Gordon et al., tDCS was delivered alongside a different form of neurocognitive training: approach bias modification. Approach bias modification training aims to alter approach bias for appetitive cues, including high-calorie food cues, and has been shown to reduce

approach tendencies towards food, attention bias towards food, and craving for food in BN and BED (Brockmeyer et al., 2017). It is possible that approach bias modification training is not the optimal adjunct to tDCS treatment in BED, or that ABMT produces greater change in BED symptoms than approach bias modification.

Second, Gordon et al. used a lower dose of tDCS than the TANDEM trial (6 sessions over 3 weeks versus 10 sessions over 2 weeks). The higher number of sessions delivered during TANDEM, coupled with the shorter time between sessions (week-daily versus twice weekly) may have led to a more potent effect of treatment on BED symptoms. Alternatively, the requirement that participants commit more time to treatment may have led to the recruitment of individuals who were more motivated or committed to change, and this positively impacted outcomes from treatment. Indeed, motivation for change and engagement with treatment is a well-established predictor of treatment outcome in the therapeutic setting (Hilbert et al., 2020).

Third, the environments within which participants completed treatment and assessment were enormously different. In Gordon et al., treatment and assessment sessions were delivered in the controlled laboratory environment, whereas in TANDEM all activities were undertaken at home. The home environment is filled with cues that a person may associate with their binge eating behaviour and it is an environment where they typically feel comfortable and relaxed. It is possible that these factors contributed to the promising effects of tDCS with ABMT on BED symptoms. Indeed, the effects of tDCS outlast the stimulation period by up to 45 minutes, so the activities that the person undertakes immediately after treatment may influence the outcome from treatment. However, modest findings by Gordon et al. may also reflect their assessment of outcomes under controlled conditions, where risk of bias is minimal. Indeed, it is noteworthy that Gordon et al. used a double-blind study design.

Finally, differences in findings may relate to the different ways in which tDCS was administered: self-administration versus administration by a technician. Neuronavigation is not available for tDCS, so regardless of the mode of administration, questions remain about whether the stimulation has reached the cortical target. Self-administered tDCS uses a “one-size-fits-all” cap to place electrodes on the scalp, so it is likely that there is a high level of variability in the cortical targets affected by stimulation. In contrast, technician-led tDCS uses

somewhat more robust techniques to identify the location of the scalp which corresponds to the cortical target (e.g., the 10-20 method or EEG co-ordinates). Both approaches are thwart with limitations, and studies have shown that without neuronavigation cortical target identification is extremely unreliable (Dunlop et al, 2021). Nevertheless, it is possible that differences in findings may relate to differences in the cortical structures effected by the stimulation.

7.3 General Strengths and limitations

The principal strength of the studies presented in this thesis relates to the novelty of the research conducted. To the best of our knowledge, the randomised sham-controlled trial described here was the first to use self-administered tDCS in adults with EDs. Our investigation of at-home self-administered tDCS was timely. The COVID-19 pandemic prompted an abrupt shift away from face-to-face interventions and towards at-home treatment and, in doing so, highlighted the need to rapidly expand our offering of remotely delivered care. In parallel, the arrival of hospital-grade tDCS devices intended for self-administration by the patient is a further prompt to take studies of tDCS beyond the lab and into the home. This need is echoed by patients with EDs, who, despite feeling hopeful about the promise of a new class of treatments and enthusiastic about the concept of "brain directed" interventions, indicate that the greatest barrier to neuromodulation as a treatment is the significant burden involved (i.e., the time required to attend lengthy and frequent sessions at a hospital or lab)(Dalton et al., 2022; Gordon, Williamson, et al., 2021). Thus, the development of brain-directed interventions which circumnavigate or minimise these barriers to treatment is a priority for patients/participants.

The TANDEM trial was also the first trial to evaluate an intervention that integrated tDCS with ABMT and, in doing so, it provided a logical addition to a growing literature on tDCS with neurocognitive training in EDs and, more broadly, psychiatry. Here, the feasibility design was a strength as it allowed us to canvas interest in this approach by assessing recruitment, retention to follow-up, and treatment adherence, and evaluate participant views about the treatment, without overemphasising the need to evaluate treatment effectiveness. However, tDCS may also pair well with other neurocognitive interventions (e.g., tDCS with inhibitory control training or mindfulness-based treatment), and we expect a portfolio of

feasibility studies to critically inform the design of a future large scale trial of tDCS with adjunct neurocognitive training in BED.

The diverse sample included in the TANDEM trial is also a key strength. As all components of this trial were delivered remotely, we were able to cast an extremely wide net during recruitment. This likely contributed to the age, geographic and demographic diversity of individuals in our sample, although male representation was extremely low ($n_{male} = 2$). Bolstering male representation in future trials will be necessary to improve representativeness: it the estimated that prevalence of BED is approximately equal for biological males and females (Galmiche et al., 2019). Nevertheless, this diversity fortifies our findings of good feasibility and intervention acceptability. However, adoption of the fully remote design also required that we sacrifice control over factors that might introduce unwanted variability or bias during outcome assessment. For example, during lab-based assessments, researchers can control a myriad of factors that might influence participant responses (e.g., ambient noise, interruptions, and lighting) and they can make use of instruments which reduce reliance on self-report data (e.g., bioimpedance analysis may be used to assess physical health metrics). In contrast, at-home assessments are vulnerable to interruption and there are few alternatives to self-report data for physical health metrics.

The fully remote research design was made necessary by the COVID-19 pandemic, and it is important that the potential impacts this had on trial feasibility be considered. It is now well documented that among people with a history of or living with an ED, re-occurrence and deterioration of symptoms during COVID-19 was common (Giel et al., 2021; Castellini et al., 2020; Clark Bryan et al., 2020; Schlegl, Maier et al., 2020; Schlegl, Meule et al., 2020; Termorshuizen et al., 2020), and that during this time access to treatment and support was limited, particularly for people with BED (Weiissman et al, 2020; Zipfel et al., 2022). This may have positively influenced willingness to take part in a trial of a new treatment for BED and influenced views about the acceptability of completing treatment at home. Indeed, people were mandated to stay home and many continued to work from home and/or spend more time at home, even after public health guidance around social contact was relaxed. During COVID-19, public knowledge of the role of science in clinical innovation was at an all- time high: daily briefings about progress towards a vaccine

may have inspired others to give their time to research so that they could aid discovery and alleviate suffering. Similarly, profound isolation may have motivated people to take part in trials like TANDEM: those who took part in TANDEM benefited from social contact with the researcher delivering treatment almost every day, and for some, this was the only contact they had with the outside world. COVID-19 also left many with grave concerns about their financial security, with many unable to work and/or receiving a smaller income than they needed to meet the costs of daily life. Although the financial incentive to take part in TANDEM was modest (£50), bolstering income during a period of immense financial strain may have been a key contributor to some participants decision to take part. In light of the probable impact of COVID-19 on recruitment and acceptability, it may be warranted to replicate these feasibility findings under "life-as-usual" conditions, so that informed decisions can be made about the feasibility of future large-scale trials.

Relatedly, the fully remote research design made necessary by COVID-19 influenced outcome measure selection. In particular, our use of the visual probe task with webcam based eye-tracking may be viewed as both a strength and a limitation to the collection of studies presented in this thesis. On the one hand, it has been proposed that eye-tracking methods offer more reliable assessment of AB and provide greater insight into the components of biased attention (Waechter et al., 2014), however, as demonstrated by the small number of studies that used eye-tracking to assess AB towards emotional stimuli in our meta-analytic review (Chapter 2), many studies continue to use on less reliable instruments when assessing AB (e.g., reaction time indices). This may reflect barriers to using eye-tracking, such as limited access to shared equipment, high costs for equipment acquisition and maintenance, lack of portability, and labour intensive set-up procedures. As such, consideration for a novel, scalable and affordable webcam-based eye-tracking solution was warranted.

On the other hand, relative to laboratory standard eye-tracking systems, webcam-based technologies have limited capabilities, and for this reason, we were unable to assess several components of biased attention in this thesis (e.g., initial fixation bias, or difficulties disengaging with food stimuli during the early stages of attention processing). Indeed, this limited our ability to characterise AB towards food in obesity with and without BED (Chapter 3) and our insight into intervention effects on food-related AB in the TANDEM trial (Chapter 6). Hence, while we expect that

webcam-based eye-tracking will be a useful tool for assessing attention-related processes, including AB, in the future, our findings indicate that this technology is not yet robust enough for use in clinical trials.

7.4 Future directions

The findings reported in this thesis provide a valuable "first-look" at the potential clinical efficacy of self-administered tDCS with ABMT and highlight gaps in the literature that should be addressed.

There is a need to clarify the effect of neuromodulation on AB, and attention control more broadly. Findings from our meta-analytic review of the effects of NIBS on AB in the context of emotion highlight the need for greater consistency in the literature. In particular, our understanding of the effect would be improved by studies which use "best practice" paradigms to directly assess AB (e.g., eye-tracking) in populations with baseline AB (e.g., clinical or sub-clinical samples) and using brief multi-session study designs (e.g., 3 sessions). Additionally, more studies using the same stimulation parameters would improve cross-study comparability and, therefore, improve the quality of future meta-analyses.

The literature would also be improved by studies that clarify the extent to which attention towards food in people with BED is distinct from that observed in people with overweight and obesity. In particular, studies which manipulate appetitive motivational factors in people with obesity with and without BED will help to characterise AB in both populations. Similarly, studies using free-viewing paradigms with lab-based eye-tracking will improve our knowledge of the temporal dynamics of AB towards food and help to identify the processes most critically involved in perpetuating maladaptive eating behaviours.

This trial aimed to assess the feasibility of a fully powered RCT of tDCS with ABMT intervention efficacy in BED, and to provide preliminary data about clinical efficacy which could inform sample size. Based on TANDEM findings, a conservative estimate of the sample size needed to detect a difference between groups would use the smallest effect size for OBE change score observed in the TANDEM trial. This was observed when comparing tDCS with ABMT and ABMT only ($d = -0.21$). Based on this approach, a future large scale RCT with 4 arms (real tDCS with ABMT, sham tDCS with ABMT, ABMT only, and WL), a significance

criterion of α = .05 and power = .80, the minimum sample size needed to detect a difference between the real and sham groups with this effect size is N = 676 (169 participants per group). Assuming drop-out rates were low, as in this feasibility trial (3.6% drop out rate), a total of 703 participants would need to be recruited. If this estimate were based on the effect size observed when comparing real tDCS with ABMT with sham tDCS with ABMT, a smaller sample size could be used (N = 92). Given the large sample size needed to use the same study design, future trials could consider an RCT with two arms (real tDCS with ABMT and sham tDCS with ABMT) or three arms (as previously plus WL). Using the TANDEM effect size for OBE change score comparing real tDCS with ABMT with sham tDCS with ABMT, a two arm trial with a significance criterion of α = .05 and power = .80, the minimum sample size needed to detect a difference between the real and sham groups with this effect size is N = 66 (33 participants per group). For a three arm RCT, a minimum of 81 participants would be needed (27 per group).

Future investigations of at-home self-administered tDCS with ABMT are also encouraged, however, these should address the limitations identified during the TANDEM trial. First, TANDEM was conducted during the COVID-19 pandemic, and at this time, it was not feasible to blind the experimenter to real/sham allocation. Future studies should implement a double-blind study design to reduce the risk of experimenter bias. Second, future trials should use a hybrid design which allows them to make use of the benefits of lab-based assessment, whilst also retaining the remote treatment model. This approach would reduce reliance on self-report data and allow for AB to be assessed using specialist eye-tracking equipment, as opposed to webcam based eye-tracking software. Relatedly, given the similarities between ABMT and the visual probe task, future studies should consider using alternative instruments to assess change in AB over time. We recommend free-viewing paradigms as these have been shown to have superior psychometric properties in both clinical (e.g., Soleymani, et al., 2020) and non-clinical populations (e.g., Veerapa et al., 2020), and they allow for the assessment of AB at different stages of attention processing.

Including functional neuroimaging during outcome assessment will also be vital to informing cortical target selection for future studies applying neuromodulation, and for clarifying the neural changes which underlie therapeutic effects associated with

neuromodulation. For example, functional magnetic resonance imaging during the attention network task with food cues may be used to assess whether treatment is associated with changes in neural activation during the alerting, orienting and re-orienting stages of attention processing (Mercado et al., 2023; Yokum et al., 2011). Alternatively, functional neuroimaging during the Food Choice Task may provide insight into how the intervention has influenced food-directed attention and goal-directed decision making in the context of food (Dalton et al., 2020; Foerde et al., 2018). Future studies would also benefit from the addition of outcomes related to food consumption. For example, food-diaries could be integrated with daily treatment sessions, or lab-based assessments could incorporate brief measures like the bogus taste test (Robinson et al., 2017). Finally, longer follow-up periods (e.g., 1 year) would be of use.

Studies of the feasibility, acceptability, and therapeutic effects of tDCS with other neurocognitive trainings or brain-directed interventions is also recommended. A number of neurocognitive interventions have been developed to target maintenance mechanisms implicated in BED, although findings relating to their clinical efficacy have been mixed and questions remain about dose, personalisation, and patient/participant selection. Inhibitory control training may produce reductions in binge eating behaviour and has shown promise as a stand-alone treatment for binge-type EDs (Turton et al., 2019; Chami et al., 2021). During inhibitory control training, participants learn to suppress a pre-potent response to salient stimuli, such as food, and, with repetition, the inhibition response is learned, repeated, and perhaps translated to real-life (Jones et al., 2016). Like ABMT, inhibitory control training is a good candidate for delivery alongside tDCS: it directly targets "top-down" cognitive control processes involving the DLPFC, it is easy to administer, and can be tailored to the individual (e.g., by personalising the stimuli used during the training). Outcomes from a feasibility trial of lab-based tDCS with inhibitory control training are expected (Giel, Schag, et al., 2022).

In light of promising findings from a recent study comparing outcomes from mindfulness-based treatment and ABMT in adults with obesity with and without BED, tDCS with adjunct mindfulness-based treatment may also be beneficial. Indeed, recent studies in depression and substance use disorders have reported that tDCS with adjunctive mindfulness-based treatment is feasible and acceptable, and

preliminary findings in depression suggest the intervention may produce superior outcomes relative to stand-alone tDCS treatment (Monnart et al., 2019). Given the role of emotion regulation difficulties in the maintenance of BED (Leehr et al., 2015), it is also possible that adjuncts to tDCS that target emotion regulation may have therapeutic effects. Emotion regulation has been conceptualised as a cognitive control function, wherein successful emotion regulation relies upon the orchestration of "top down" control in the context of a strong "bottom up" response (Oschner et al., 2013). Interventions targeting emotion regulation are commonly applied to the treatment of BED (e.g., dialectical behaviour therapy; Hilbert et al., 2019), and it is conceivable that brief programs which aim to increase utilisation of "adaptive" emotion regulation techniques, including reappraisal and cognitive restructuring, may have benefit and be suitable for delivery during neuromodulation. Indeed, a recent trial in a transdiagnostic sample has demonstrated that outcomes from cognitive restructuring may be enhanced by transcranial magnetic stimulation (Neasciu et al., 2021).

There is also a need to deepen our understanding of who benefits most from which approach, and the ways in which neuromodulation augments adjunct treatment. Presently, we have a limited knowledge of how tDCS effects brain functioning or the parameters of greatest importance to treatment response. This calls for studies examining how therapeutic effects differ when key parameters are changed (e.g., dose, intensity, current flow, cortical target, and adjunct versus no adjunct), as well as studies that pair stimulation with neuroimaging, so that we can gain insight into the effects of stimulation on brain function in real time. Relatedly, there is a need to establish optimal parameters for tDCS, or indeed establish guidelines for personalising tDCS parameters to optimise treatment. Additionally, these studies should aim to identify individual biological, cognitive and clinical markers of intervention response so that optimal parameters may be selected on an individual basis.

7.5 Overall conclusion

The research presented in this thesis evaluated the literature on NIBS and AB and examined the potential for self-administered tDCS with ABMT as an intervention for adults with BED. In chapter 2, our meta-analytic review concluded that evidence for an effect of tDCS on AB is lacking, however, studies in clinical populations generally reported a significant effect of NIBS on AB towards emotion. This suggests that the therapeutic effects associated with NIBS targeting the DLPFC may be driven by improvements in cognitive control of attention (i.e., reduced AB). Chapter 3 reported that participants with obesity with and without BED showed an AB towards high-calorie food cues, and that AB towards high-calorie food cues was related to craving for food, although this correlation was substantially stronger in BED. This finding is consistent with those reported in previous studies and substantiates the selection of AB towards food as a mechanistic target for treatment in BED. Chapters 4-6 presented a randomised sham-controlled trial of self-administered tDCS with ABMT. Overall, findings relating to recruitment and retention support protocol feasibility, and excellent acceptability ratings indicate that the intervention was well-liked by participants. Preliminary findings relating to clinical efficacy were also promising; tDCS with ABMT produced pronounced improvement in BED symptoms and there was tentative evidence to suggest that real tDCS with ABMT may produce superior outcomes from treatment, relative to sham tDCS with ABMT and ABMT only. Moreover, treatment was associated with significant reductions in AB towards high-calorie food which were maintained at follow-up. Taken together, the work presented in this thesis indicate that tDCS with ABMT is a promising novel approach to treatment and future trials of tDCS with ABMT and related neurocognitive training programmes are encouraged.

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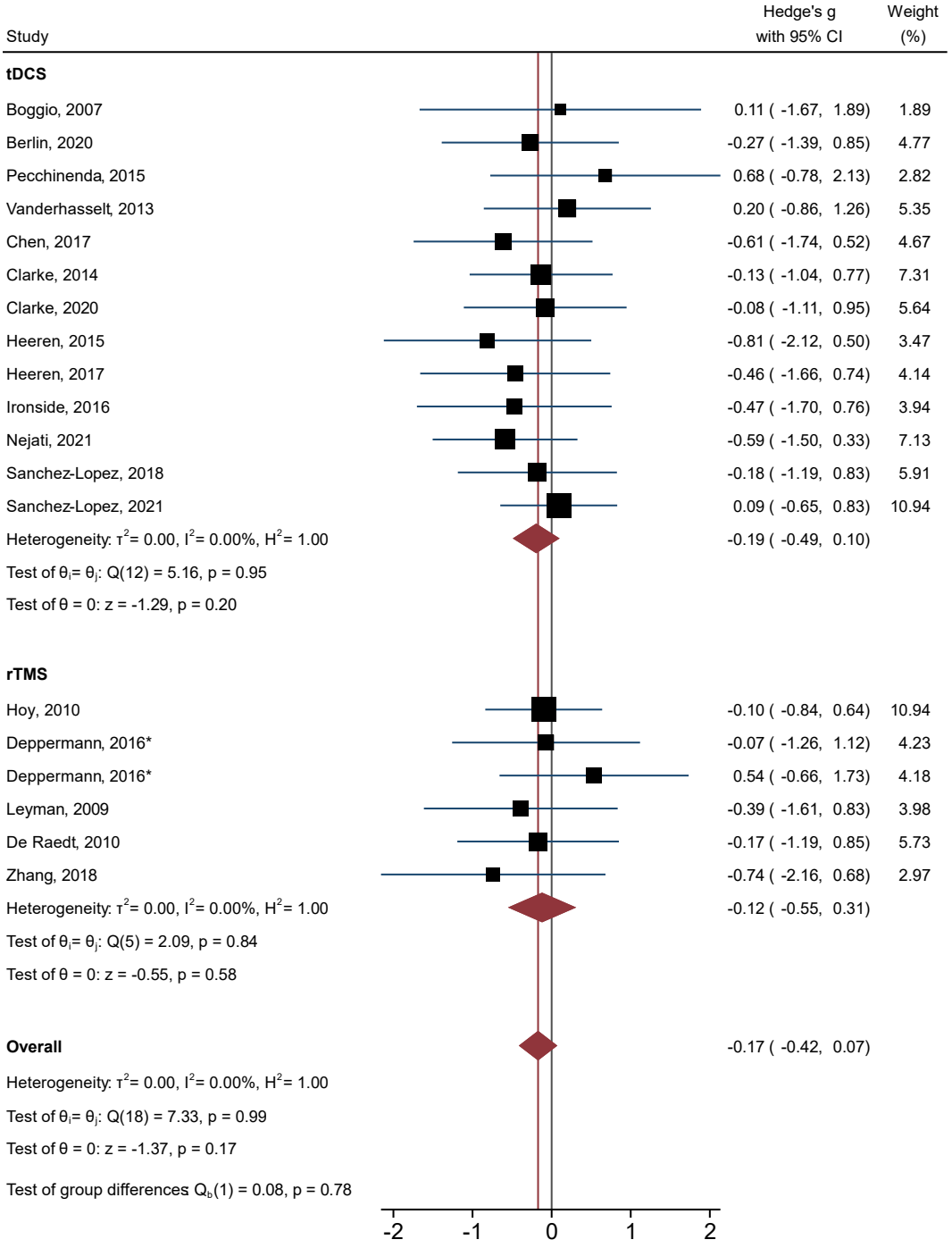
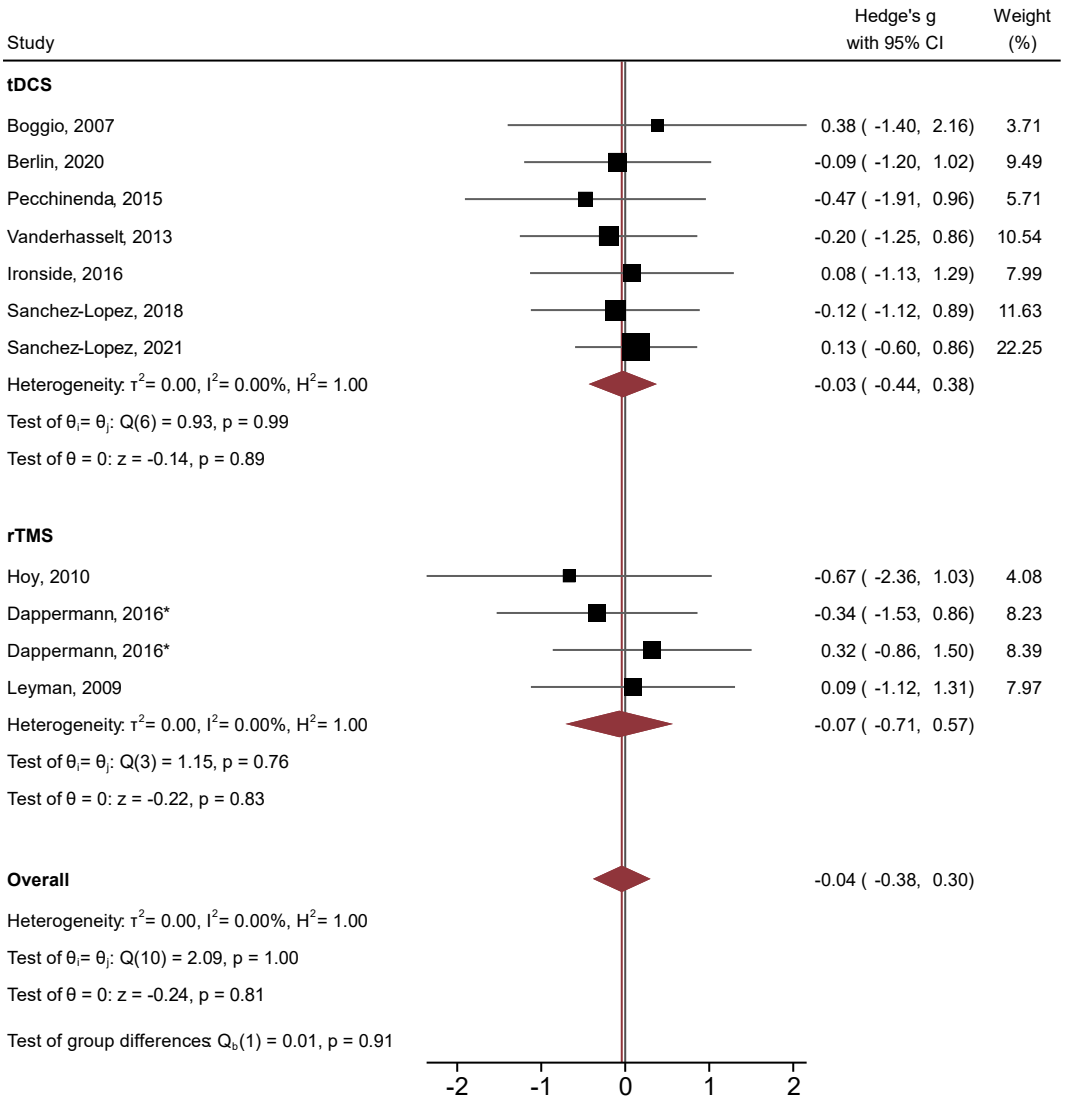
Appendices

Appendix A. Supplementary results

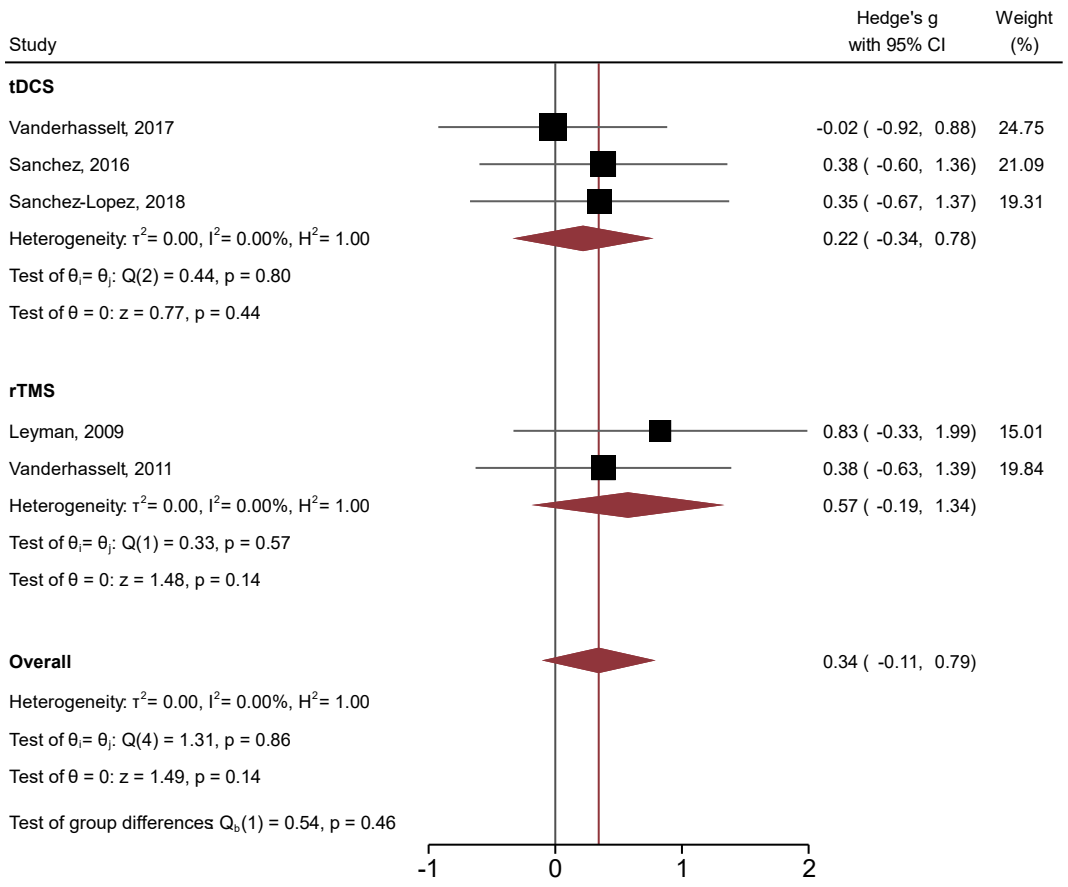
Appendix A.1 Forest plot summary of effect sizes and confidence intervals for studies examining the effect of excitatory stimulation of the left DLPFC on negative attention bias.



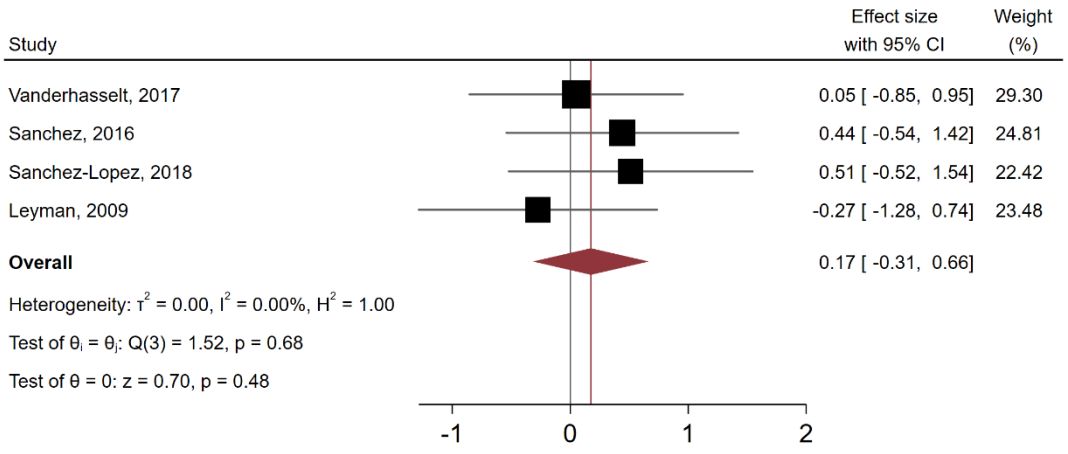
Appendix A.2. Forest plot summary of effect sizes and confidence intervals for studies examining the effect of excitatory stimulation of the left DLPFC on positive attention bias.



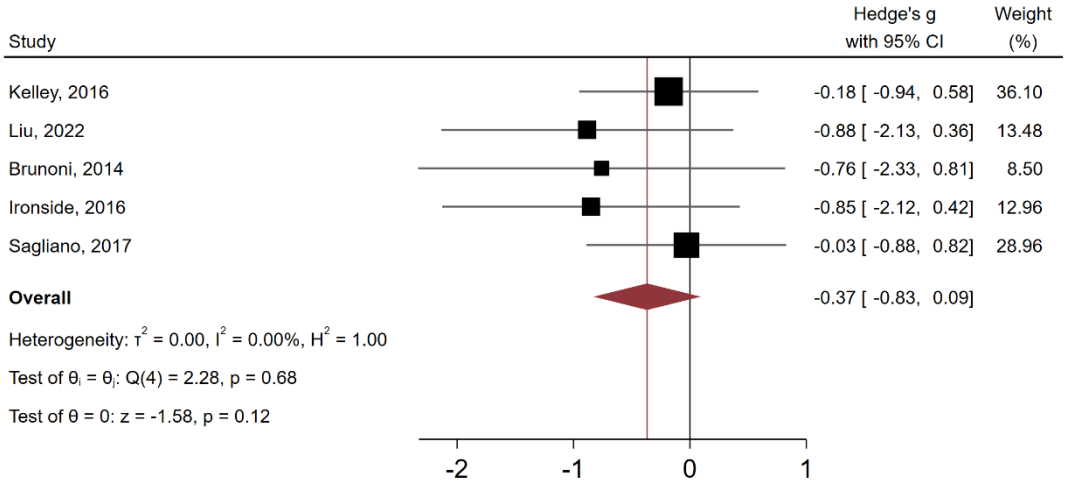
Appendix A.3. Forest plot summary of effect sizes and confidence intervals for studies examining the effect of excitatory stimulation of the right DLPFC on negative attention bias.



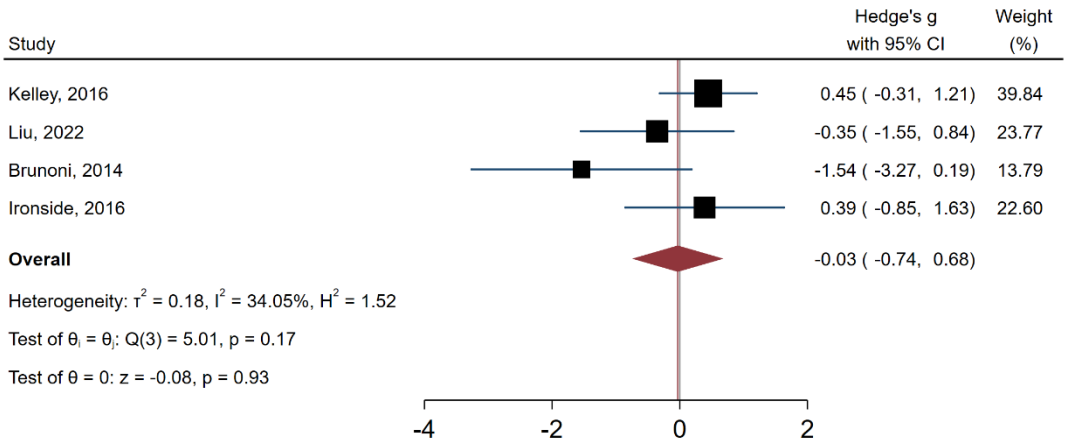
Appendix A.4. Forest plot summary of effect sizes and confidence intervals for studies examining the effect of excitatory stimulation of the right DLPFC on positive attention bias.



Appendix A.5. Forest plot showing the effect of bilateral tDCS using the anode left/cathode right electrode montage on negative attention bias.



Appendix A.6. Forest plot showing the effect of bilateral tDCS using the anode left/cathode right electrode montage on positive attention bias.



Appendix A.7. Cochrane risk of bias assessment by domain for each study using a between-subjects study design

Appendix A.8. Cochrane risk of bias assessment by domain for each study using a crossover design

Appendix A.9. TANDEM demographic characteristics

	Whole Sample *n* (%)	**Real tDCS+ABMT** *n* (%)	**Sham tDCS+ABMT** *n* (%)	**ABMT Only** *n* (%)	**Wait** *n* (%)
Highest Level of Education Achieved					
University	56 (68.29)	16 (80.0)	14 (70.00)	13 (65.00)	13 (68.42)
A or AS Levels	14 (17.07)	3 (15.0)	2 (10.00)	4 (20.00)	2 (10.53)
GCSE	7 (8.54)	1 (5.0)	4 (20.00)	1 (5.00)	1 (5.26)
Other tertiary	5 (6.10)	0	0	2 (10.00)	3 (15.79)
Ethnicity					
White	75 (91.50)	19 (95.0)	19 (95.00)	17 (85.00)	17 (89.47)
Black	3 (3.66)	0 (0.00)	0 (0.000	2 (10.00)	1 (5.26)
Asian	3 (3.66)	0 (0.00)	1 (5.00)	1 (5.00)	1 (5.26)
Latino	1 (1.20)	1 (5.0)	0	0	0
Marital Status					
Single	23 (28.05)	5 (25.00)	4 (20.00)	5 (25.00)	8 (42.11)
Dating	10 (12.20)	5 (25.00)	1 (5.00)	2 (10.00)	2 (10.53)
Married*	38 (46.34)	7 (35.00)	13 (65.00)	11 (55.00)	5 (26.32)
Divorced	7 (8.54)	1 (5.00)	2 (10.00)	2 (10.00)	2 (10.53)
Other	4 (4.88)	2 (10.00)	0	0	2 (10.53)

* Includes civil partnership and equivalent long-term relationships. SD, standard deviation; GCSE, General Certificate of Secondary Education; A, advanced; AS, Advanced Subsidiary; BMI, body mass index; tDCS, transcranial direct current stimulation; ABMT, attention bias modification training.

Appendix A.10. Mean scores for clinical outcome measures at post-treatment (T1) and follow-up (T2) by group

	Real tDCS+ABMT			Sham tDCS+ABMT			ABMT Only			WL		
	n	$\bar{X}$	SD	*n*	$\bar{X}$	SD	*n*	$\bar{X}$	SD	*n*	$\bar{X}$	SD
Change from Baseline (T0) to Post-treatment (T1)												
BMI	20	38.52	6.46	19	39.21	8.62	20	41.62	8.52	17	40.56	6.55
EDE-Q Global	20	3.00	0.83	19	3.40	1.03	20	3.62	0.99	17	4.07	1.14
Monthly OBEs	20	10.95	5.93	19	13.26	15.23	20	12.45	8.81	17	18.29	7.88
DASS-21 Depression	20	13.50	8.31	19	13.47	8.87	20	14.00	10.24	17	14.82	10.91
DASS-21 Anxiety	20	5.50	4.58	19	7.89	7.84	20	7.50	6.15	17	9.06	8.72
DASS-21 Stress	20	12.80	7.15	19	14.00	6.32	20	13.30	6.88	17	16.47	8.41
DASS-21 Total	20	31.80	16.86	19	35.37	20.59	20	34.10	18.69	17	40.71	23.54
FCQ-Tr Total	20	49.40	14.46	19	50.95	15.57	20	51.75	14.92	17	63.00	8.16
DERS	20	27.25	18.49	19	33.58	17.10	20	26.35	14.73	17	31.53	16.79
CIA	20	1.22	0.51	19	1.35	0.46	20	1.32	0.56	17	1.47	0.63
Change from Baseline (T0) to Follow-Up (T2)												
BMI	20	37.73	6.32	19	39.05	8.61	19	40.39	6.84	17	40.57	6.57
EDE-Q Global	17	1.78	0.76	17	2.82	0.90	17	2.27	0.98	17	3.90	1.25
Monthly OBEs	17	6.25	6.01	17	12.00	14.29	17	9.94	10.00	17	19.06	5.79
DASS-21 Depression	17	7.41	5.42	17	12.00	8.09	17	14.82	10.30	17	15.53	11.67
DASS-21 Anxiety	17	6.35	6.37	17	8.35	6.33	17	5.88	6.54	17	9.41	8.57
DASS-21 Stress	17	12.47	8.65	17	14.00	7.87	17	12.00	7.58	17	16.35	7.57
DASS-21 Total	17	26.24	18.00	17	34.35	19.90	17	32.94	22.87	17	41.29	23.18
FCQ-Tr Total	17	41.00	13.67	17	48.82	16.22	17	46.41	16.63	17	63.47	7.45
DERS	17	22.47	14.86	17	28.50	15.26	17	28.18	12.01	17	32.59	7.41
CIA	17	0.84	0.35	17	1.18	0.55	17	1.37	0.74	17	1.54	0.57

Abbreviations (in alphabetical order): ABMT, attention bias modification training; BMI, body mass index; CIA, Clinical Impairment Assessment; DASS-21, Depression, Anxiety and Stress Scale – 21 items; DERS, Difficulties with Emotion Regulation Scale; EDE-Q; Eating Disorders Examination Questionnaire; FCQ-Tr, Food Craving Questionnaire-Trait reduced version; *n,* number of observations, OBEs, objective binge eating episodes; SD, standard deviation, tDCS, transcranial direct current stimulation; WL, wating list; $\bar{X}$, sample mean.

Appendix A.11. Mean change scores* for clinical outcome measures from baseline to post-treatment and follow-up.

	Real tDCS+ABMT			Sham tDCS+ABMT			ABMT Only			WL		
	n	$\bar{X}$	SD	*n*	$\bar{X}$	SD	*n*	$\bar{X}$	SD	*n*	$\bar{X}$	SD
Change from Baseline (T0) to Post-treatment (T1)												
BMI	20	-0.48	0.59	19	-0.36	0.56	20	0.14	0.49	17	0.01	0.17
EDE-Q Global	20	-1.00	0.68	19	-0.60	0.37	20	-0.58	0.67	17	0.09	0.40
Monthly OBEs	20	-8.63	8.35	19	-6.11	7.14	20	-8.60	7.28	17	-1.82	6.53
DASS-21 Depression	20	-4.20	7.70	19	-1.05	5.26	20	-3.80	6.35	17	-0.47	6.30
DASS-21 Anxiety	20	-2.10	4.83	19	-0.21	2.90	20	-1.51	5.10	17	1.65	7.01
DASS-21 Stress	20	-5.90	9.06	19	-2.11	5.71	20	-5.20	6.14	17	0.12	5.77
DASS-21 Total	20	-12.60	18.31	19	-3.37	9.09	20	-10.56	12.15	17	1.65	13.25
FCQ-Tr Total	20	-14.50	13.81	19	-9.58	14.08	20	-12.55	13.28	17	-0.12	6.30
DERS	20	-9.15	7.30	19	3.68	10.86	20	-6.25	12.78	17	2.59	8.75
CIA	20	-0.27	0.55	19	-0.08	0.48	20	-0.33	0.39	17	-0.03	0.33
Change from Baseline (T0) to Follow-Up (T2)												
BMI	20	-1.28	1.48	19	-0.52	0.66	19	0.67	0.53	17	0.02	0.14
EDE-Q Global	17	-2.29	1.10	17	-1.25	0.79	17	-2.01	0.95	17	-0.08	0.65
Monthly OBEs	17	-13.06	12.33	17	-7.41	6.34	17	-10.47	12.02	17	-1.06	3.91
DASS-21 Depression	17	-11.41	12.10	17	-1.06	6.79	17	-3.41	6.79	17	0.24	6.59
DASS-21 Anxiety	17	-2.12	5.07	17	-0.12	4.39	17	-2.71	5.57	17	2.01	7.11
DASS-21 Stress	17	-6.24	9.72	17	-2.35	5.97	17	-6.35	6.05	17	0.12	6.04
DASS-21 Total	17	-19.76	23.38	17	-3.53	14.12	17	-12.24	10.63	17	1.65	13.25
FCQ-Tr Total	17	-22.11	14.21	19	-11.65	17.16	20	-16.35	17.72	17	0.35	5.92
DERS	17	-12.94	12.54	17	-1.13	13.60	17	-4.12	13.87	17	3.64	8.37
CIA	17	-0.73	0.66	17	-0.27	0.54	17	-0.31	0.62	17	-0.01	0.43

* Post-treatment/follow-up scores minus baseline scores. Abbreviations (in alphabetical order): ABMT, attention bias modification training; BMI, body mass index; CIA, Clinical Impairment Assessment; DASS-21, Depression, Anxiety and Stress Scale – 21 items; DERS, Difficulties with Emotion Regulation Scale; EDE-Q; Eating Disorders Examination Questionnaire; FCQ-Tr, Food Craving Questionnaire-Trait reduced version; *n,* number of observations, OBEs, objective binge eating episodes; SD, standard deviation, tDCS, transcranial direct current stimulation; WL, wating list; $\bar{X}$, sample mean.

Appendix A.12. Reaction times for congruent and incongruent trials on the visual dot probe task and total fixation times for food and non-food items at baseline, post-treatment, and follow-up (means and standard deviations)

	Real tDCS+ABMT (n = 15)			**Sham tDCS+ABMT** (n = 14)			**ABMT Only** (n =14)			**WL** (n = 11)		
	T0	T1	T2	T0	T1	T2	T0	T1	T2	T0	T1	T2
Reaction Times												
Congruent trials												
Food (Overall)	507.13	515.77	489.04	499.20	482.68	468.61	529.31	495.86	509.60	509.77	506.97	497.52
	(56.43)	(93.47)	(59.96)	(66.05)	(73.67)	(55.390	(177.59)	(82.43)	(67.160	(104.34)	(72.08)	(39.95)
HC Trials	510.92	540.72	496.38	504.52	502.30	474.91	518.87	503.71	515.82	511.16	512.51	512.36
	(72.94)	(130.77)	(59.49)	(73.42)	(74.54)	(52.68)	(177.96)	(91.52)	(79.21)	(102.83)	(73.02)	(49.38)
LC Trials	502.21	492.89	479.90	500.89	484.38	476.05	539.99	495.61	495.34	513.86	505.32	502.65
	(45.78)	(75.00)	(72.73)	(64.46)	(73.03)	(57.11)	(181.00)	(78.17)	(84.91)	(108.34)	(77.68)	(34.09)
Incongruent Trials												
Food (Overall)	522.39	511.28	481.35	514.31	480.80	473.35	543.81	502.66	518.84	523.39	523.06	513.13
	(70.86)	(83.42)	(64.84)	(68.92)	(73.41)	(67.01)	(183.51)	(89.59)	(82.72)	(103.11)	(78.31)	(59.36)
HC Trials	527.85	522.80	462.19	518.64	488.27	472.09	537.35	507.08	520.21	528.07	533.59	532.27
	(61.12)	(120.66)	(72.40)	(69.18)	(74.70)	(67.15)	(172.37)	(82.57)	(89.95)	(100.99)	(97.00)	(80.14)
LC Trials	514.90	502.15	501.40	514.81	485.63	487.33	550.13	504.94	511.73	524.25	513.69	511.83
	(62.17)	(72.62)	(72.59)	(75.07)	(73.38)	(69.83)	(197.27)	(96.49)	(98.45)	(111.62)	(68.18)	(48.25)
Total Fixation Times												
Neutral Items	1258.79	1222.98	1215.16	1272.82	1235.81	1242.09	1311.15	1233.84	1248.33	1212.66	1206.05	1208.63
	(102.61)	(97.46)	(115.31)	(117.65)	(268.91)	(184.78)	(154.22)	(187.94)	(156.57)	(156.43)	(168.31)	(179.64)
Food (Overall)	1544.75	1487.40	1501.35	1526.76	1489.49	1507.98	1505.73	1476.61	1481.73	1523.38	1530.83	1511.50
	(123.49)	(110.94)	(72.28)	(159.87)	(165.66)	(243.24)	(121.53)	(127.37)	(155.82)	(150.53)	(151.70)	(151.91)
HC Stimuli	1514.76	1304.08	1330.97	1537.82	1437.64	1419.78	1509.41	1463.78	1507.18	1521.85	1542.68	1518.32
	(131.85)	(221.09)	(273.72)	(173.09)	(267.35)	(400.07)	(158.60)	(137.48)	(163.34)	(157.27)	(223.35)	(199.77)
LC Stimuli	1541.21	1620.00	1642.96	1498.95	1533.77	1578.08	1470.67	1458.52	1484.52	1492.45	1510.39	1506.52
	(144.89)	(348.57)	(344.81)	(172.05)	(193.97)	(196.02)	(106.75)	(138.56)	(141.03)	(176.02)	(151.62)	(93.20)

Abbreviations (in alphabetical order): ABMT, attention bias modification training; HC, high-calorie; LC, low-calorie; tDCS, transcranial direct current stimulation; WL, waiting list.

Appendix A.13. Bar chart summary of mean attention bias score for low-calorie food stimuli over time by group controlling for baseline BMI.

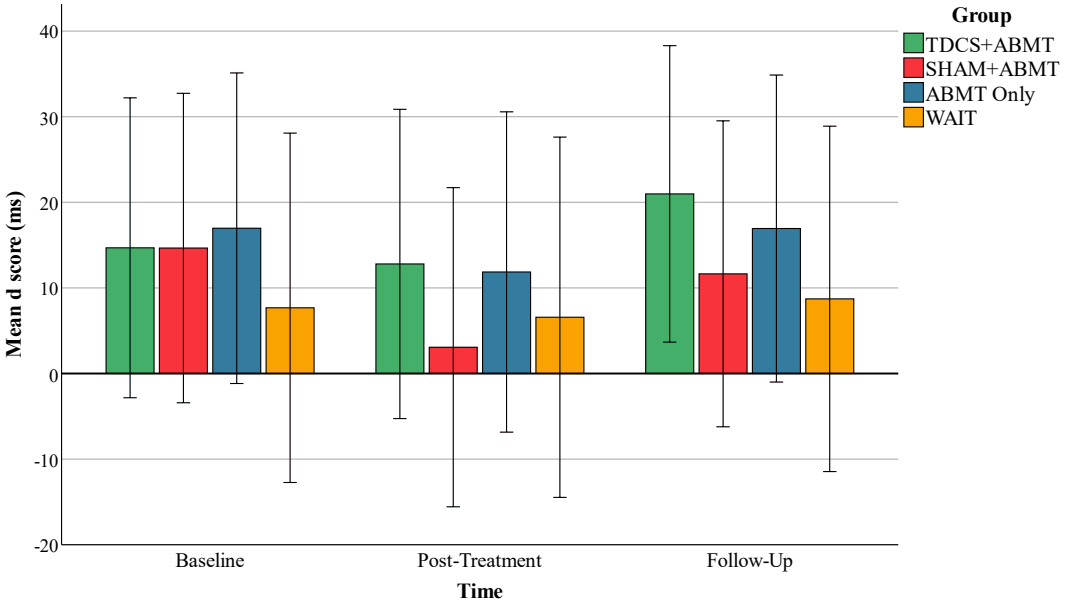


Figure legend: Error bars show 95% confidence intervals.

Appendix A.14. Bar chart summary of mean dwell bias score for low-calorie food stimuli over time by group controlling for baseline BMI.

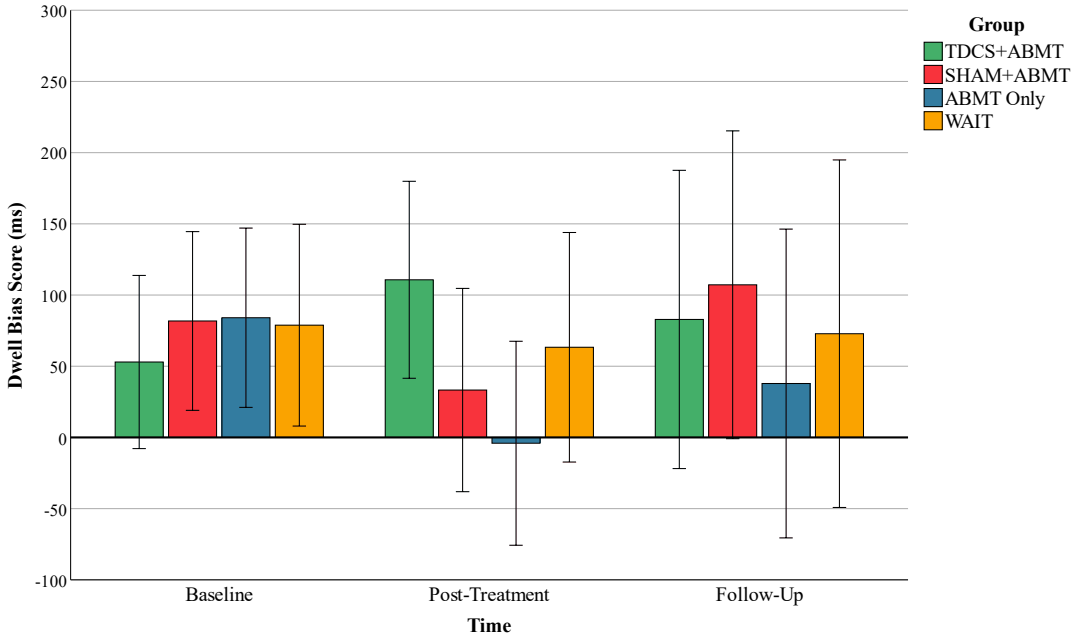


Figure legend: Error bars show 95% confidence intervals.

Appendix A.15. Correlations between attention bias towards high-calorie food and clinical outcomes over time (whole sample)

		Attention Bias Score		Dwell Bias Score	
		Post-Treatment	Follow-Up	Post-Treatment	Follow-Up
Monthly OBEs	*r*	.037	.009	-.043	-.172
	p	.791	.950	.746	.208
Food Craving	*r*	.166	.104	.037	-.111
	p	.231	.453	.785	.425
BMI	*r*	.156	.156	.031	.048
	p	.261	.260	.816	.732
EDE-Q Global	*r*	.007	.026	.015	.041
	p	.741	.341	.424	.424
DASS-21 Total	*r*	-.187	-.269	-.162	-.237
	p	.211	.244	.317	.224

Abbreviations: OBE, objective binge eating; BMI; body mass index; DASS-21, Depression, Anxiety and Stress Scale (21-item version); EDE-Q, Eating Disorder Examination Questionnaire

Appendix B. Published papers

Appendix B.1. Copy of publication included in this thesis (Chapter 4)

frontiers | Frontiers in Psychiatry

TYPE Study Protocol
PUBLISHED 03 August 2022
DOI 10.3389/fpsyt.2022.949246

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Does concurrent self-administered transcranial direct current stimulation and attention bias modification training improve symptoms of binge eating disorder? Protocol for the TANDEM feasibility randomized controlled trial

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Background: Binge eating disorder (BED) is a common and disabling problem associated with impaired cognitive control. Preliminary studies show that brain-directed treatments, including transcranial direct current stimulation (tDCS) and attention bias modification training (ABMT), improve cognitive control and alleviate symptoms of BED. When combined, tDCS may enhance the effects of ABMT, and vice versa, thereby improving treatment outcomes.

Methods: This protocol describes a feasibility single-blind randomized sham-controlled trial of concurrent self-administered tDCS and ABMT in adults with BED (The TANDEM Trial). Eighty adults with BED will be randomly assigned to one of four groups: ABMT with real or sham self-administered tDCS, ABMT only, or waiting list control. In the treatment arms, participants will complete 10-sessions of their allocated intervention over 2–3 weeks. Outcomes will be assessed at baseline (T0), immediately post treatment (T1), and 6 weeks after end of treatment (T2), and at comparable timepoints for participants in the waitlist control group. Feasibility will be evaluated by assessing recruitment/retention rates and blinding success. Acceptability will be assessed quantitatively *via* participant ratings and qualitatively *via* semi-structured interviews. Episodes of binge eating at follow-up will be the primary clinical outcome and rate ratios from Poisson regression will be reported. Secondary outcomes will assess changes in ED and general psychopathology, attention bias toward high calorie foods, and executive function.

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Discussion: It is hoped that data from the trial will contribute to the development of neurobiologically informed treatments for BED, provide insights into the potential use of at-home variants of tDCS, and inform the design of future large scale trials.

KEYWORDS

eating disorders, binge eating disorder, transcranial direct current stimulation (tDCS), attention bias, neuromodulation

Introduction

Binge eating disorder (BED) is a common and disabling eating disorder (ED) affecting 1–3% of the global population (1). It is characterized by recurrent episodes of binge eating accompanied by feelings of loss of control and subsequent distress. Episodes occur in the absence of compensatory behaviors intended to prevent weight gain (2). Among individuals with BED, psychiatric and physical health comorbidities are common; nearly 80% of those diagnosed with BED will suffer from another psychiatric disorder during their lifetime (3), and up to 88% live with overweight or obesity, increasing individual risk for obesity related physical health problems (4). Consequently, the economic and quality of life burden associated with BED is substantial (5–7).

Psychotherapy [particularly cognitive behavior therapy (CBT)] and self-help interventions are recommended first-line treatments for BED (1). However, only about half of those who complete treatment report a significant reduction in, or abstinence from, binge eating in the 12-months following the end of treatment: moreover, neither treatment yields a significant or sustained reduction in weight (8). With respect to pharmacotherapy, second-generation antidepressants, anticonvulsants, and central nervous system stimulants produce short-term reductions in episodes of binge eating and are routinely used when treating BED. However, drug-driven reductions in binge eating episodes are not sustained beyond 3–6 months. Lisdexamphetamine, a central nervous system stimulant, is the only drug approved for use in the treatment of moderate-severe BED. However, the effect of the drug on ED psychopathology and mood remains unclear, and data on the long-term maintenance of effects are lacking. There are also significant risks associated with the drug's use; little is known about the effects of long-term administration, and rates of adverse events and premature discontinuation of the drug were elevated in RCTs (4, 8). It is possible that combining psychotherapy with pharmacotherapy may produce superior outcomes from treatment, however, findings from a recent meta-analysis yielded minimal support for this hypothesis; of the 12 included trials, only two reported that combined treatment enhanced binge eating and weight outcomes, both of which used anticonvulsant medications, and only two reported modest improvements in weight loss, but not binge eating, outcomes, both of which used the weight-loss medication, Orlistat (9).

It is widely agreed that novel treatments informed by neurobiological models of illness are needed (10). Current models propose that emotion dysregulation, elevated food cue reactivity, and executive dysfunction, are central to the etiology and maintenance of BED (11–16). These difficulties may indicate a broad impairment in cognitive control, and therefore aberrant functioning of the brain's cognitive control network. Cognitive control is the ability to orchestrate thought and action in accordance with internal goals and relies on prefrontal brain regions (e.g., the dorsolateral prefrontal cortex [dlPFC]) and associated neural networks (17). In this framework, the affective reactivity (i.e., craving and emotional reactivity) and poor self-regulatory abilities reported in BED may be a consequence of impairments in cognitive control, and interventions which improve cognitive control may facilitate remission from BED.

Cognitive bias modification (CBM) is one tool which may be used to improve cognitive control. CBM refers to a class of interventions that use experimental paradigms to change biased cognitive processes which perpetuate maladaptive behavior (18). Attention bias modification training (ABMT) is a form of CBM which aims to alter the automatic allocation of attention toward salient cues. Food-specific variants of ABMT, which were developed for use in binge-type EDs and obesity, train individuals to avoid salient high-calorie food cues and attend to neutral and low-calorie food cues (19). Meta-analyses of RCTs in healthy volunteers have revealed that a single session of food-specific ABMT is associated with a significant short-term reduction in high-calorie food consumption (medium effect size) (20) and a significant short-term reduction in bias toward high-calorie foods (medium effect size) (21). Though few studies

Abbreviations: ABMT, Attention bias modification training; BED, Binge eating disorder; dlPFC, Dorsolateral prefrontal cortex; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ED: Eating Disorder; NIBS, Non-invasive brain stimulation; TDCS, Transcranial direct current stimulation.

have used food-specific ABMT in BED, those that have report promising outcomes from treatment. One study reported that a single session of ABMT was associated with a significant short-term reduction in subjective food craving (22). Another open feasibility trial delivered 8 weekly sessions of ABMT and reported significant post-treatment reductions in weight, ED symptoms, episodes of binge eating, and attention bias toward food, and these were sustained to 3-month follow-up (23). Thus, although data on the long-term effects of ABMT are lacking, the available evidence suggests that ABMT may improve affective regulation in the context of food (i.e., cognitive control), and may have clinical utility in BED.

Non-invasive brain stimulation (NIBS) may also be used to modify functioning of cortical regions or networks implicated in BED (24, 25). Transcranial direct current stimulation (tDCS) is a NIBS technique which may be particularly well-suited to the treatment of BED: it is a safe and well-tolerated technique which is inexpensive, portable, easy to use, and suitable for remote self-administration (26, 27). In tDCS, a constant weak direct current is applied *via* electrodes placed on the scalp to increase (anodal tDCS) or decrease (cathodal tDCS) cortical excitability. Specifically, tDCS modulates network dynamics within functionally connected areas beyond the cortical regions located beneath the electrodes. As a result, tDCS has the potential to modulate task- or symptom-specific neural networks. These changes in cortical excitability outlast the stimulation period (up to 60 min after a single-session) and, with repeated administration, may lead to lasting changes in brain function (26). In light of this, tDCS is being applied to the treatment of psychiatric disorders with moderate success, particularly in major depression (26). However, questions remain about optimal participant/patient selection, parameters for stimulation, mechanisms of action and the effects of long-term use.

Proof-of-concept studies suggest that tDCS may be effective for the treatment of binge-type EDs. In bulimia nervosa, a proof-of-concept RCT with 24-h follow-up, indicated that a single-session of right dlPFC anodal tDCS improves ED psychopathology, reduces craving for food, reduces urge to binge, and improves self-regulatory control during reward related decision making (28). In BED, a single-session RCT using right dlPFC anodal tDCS reported a short term reduction in craving for food and desire to binge eat in participants who received real tDCS (29). This finding was replicated in a sham-controlled crossover trial: following a single-session of right dlPFC anodal tDCS, short-term improvements in food-related response inhibition and craving for food were observed in participants who received real 2mA tDCS stimulation, as opposed to real-1mA or sham stimulation (30).

Two studies have examined the effect of multiple sessions of tDCS on BED symptoms. A randomized sham-controlled trial involving 32 adults examined the effect of 10 sessions of tDCS on attention bias toward food, craving for food, and cognitive flexibility (31). In this trial, tDCS was given with the anode over the left dlPFC and the cathode over the right dlPFC (2mA/20 min). Sessions were 3/week until 10 sessions had been completed. At post-treatment and 45 day follow up, real tDCS treatment was associated with a greater reduction in attention bias toward food, a greater reduction in craving for food, and an improvement in cognitive flexibility. However, effect sizes were small, and the authors acknowledged several study limitations, including a small sample ($n = 32$) and concerns about the effect of poor eye-tracker calibration on the reliability of attention bias outcomes.

Our group has also recently completed an RCT of six sessions of right-anodal tDCS targeting the dlPFC delivered over 3 weeks in adults with BED [$n = 65$, (32) for protocol]. In this trial, we examined whether symptoms of BED were improved by an intervention involving the concurrent delivery of tDCS and approach bias modification training, a form of CBM which targets approach bias toward high-calorie foods. Participants were randomly allocated to one of three study groups (approach bias modification training with real tDCS, approach bias modification training with sham tDCS, or wait-list control) and outcomes were assessed at baseline, 3-weeks post-randomization, and 7-weeks post randomization. Clinical and neurocognitive outcomes are yet to be published; however, findings from a qualitative study of the treatment experience indicate that this combined approach to treatment is tolerable and acceptable (33).

It has been suggested that the efficacy of tDCS may depend on the functional state of the brain at the time of stimulation. If this is true, then greater and longer-lasting neuroplastic effects might be achieved when tDCS and CBM co-activate a disorder-related neural network (34). This may be because, by altering the relationship between excitatory (glutamatergic) and inhibitory (GABAergic) systems in the brain (35), tDCS creates optimal conditions for memory reconsolidation, a process which may re-enforce the new learning which takes place during CBM. Similarly, CBM promotes the activation of disorder relevant brain areas, and this might enhance the effectiveness of stimulation. Consistent with this, several studies in anxiety, depression, and substance abuse disorders have reported superior outcomes from treatment when tDCS was combined with interventions which activate cognitive control regions (27, 36–38).

In summary, concurrent tDCS and food-specific CBM may be a promising treatment, or adjunct to treatment, for BED. This is because of (a) evidence suggesting that tDCS and food-specific CBM may independently produce therapeutic effects in BED, and (b) the neurobiological rationale for combining these two treatments. Moreover, with the recent arrival of tDCS devices intended for supervised self-administration, both interventions can now be safely provided in the home, thereby increasing their accessibility and scalability. Accordingly, we present the protocol for a feasibility randomized controlled trial

of concurrent at-home self-administered tDCS and food-specific ABMT in BED (The TANDEM trial).

Study aims

The primary aim of the TANDEM trial is to assess the feasibility of using 10 sessions of concurrent food-specific ABMT (henceforth, ABMT) and self-administered right-dlPFC anodal tDCS as a treatment for BED. This intervention will be compared to training in combination with sham stimulation, stand-alone training, and a "no treatment" waiting control condition. In doing so, we aim to acquire key information to inform the design of a large-scale RCT.

Specifically, we aim to:

1. estimate the rate ratio for the proposed primary outcome, change in the number of monthly episodes of binge eating from baseline to follow up. This will inform the sample size calculation for a large-scale RCT.
2. explore the feasibility of conducting a large-scale RCT of at-home self-administered concurrent tDCS and ABMT in adults with BED by assessing recruitment, attendance, and retention rates;
3. assess acceptability by examining participant ratings of treatment acceptability and tolerance, and by evaluating feedback provided during semi-structured interviews;
4. determine the best instruments for measuring primary and secondary outcomes in a full trial by examining the quality, completeness, and variability in the data.

The primary clinical endpoint will be the change in monthly episodes of binge eating from baseline to follow-up. Secondary aims will focus on evaluating changes in overall ED pathology and general psychopathology, changes in attention bias toward high-calorie foods, and changes in executive functioning from baseline to 6-weeks post treatment completion.

Methods

Reporting of this protocol is guided by the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (39) and the Consolidated Standards of Reporting Trials (CONSORT) statement extension for feasibility randomized controlled trials (40). The TANDEM trial has also been registered with the U.S. National Institute for Health (NIH) Clinical Trials database (ClinicalTrials.gov; trial identifier: NCT04424745).

Study design

TANDEM is a randomized single-blind sham-controlled feasibility trial with four parallel arms: [ABMT + real tDCS], [ABMT + sham tDCS], [ABMT only], and 8-week wait-list control. After baseline assessment (T0), participants will be randomly allocated to a study group. Those allocated to treatment groups will then complete 10 sessions of their allocated treatment over 2 weeks. Outcome measures will be completed first at baseline (T0), then again immediately after completing treatment or after 2-weeks waiting (T1), and finally 6-weeks after completing treatment, or after 8-weeks of waiting (T2). Process outcomes will also be assessed at each treatment session.

Participants

Recruitment

Recruitment for this trial began in March 2021 and ran for 12 months. Participants will be recruited from the community (*via* advertisements on social media, research participant recruitment websites, and university-managed webpages), and from the South London and Maudsley outpatient ED service.

People interested in the study will receive verbal and written information about the study rationale, aims, and methodology. Specifically, participants are told that there is tentative evidence to suggest both tDCS and ABMT may reduce craving for food and episodes of loss of control eating, and that the present study will be the first to examine whether combining these two interventions may alleviate symptoms of BED. After providing written consent, participants will be screened against inclusion and exclusion criteria.

Inclusion criteria

Participants eligible for the trial must comply with all of the following criteria at randomization:

1. Aged 18–70 years.
2. Right handed
3. Overweight or obese (body mass index (BMI) $\geq$25 kg/m^2).
4. Meet diagnostic criteria for full-syndrome BED diagnosis according to the Diagnostic and Statistical Manual 5th Edition (2013).
5. Normal or corrected to normal vision.
6. Access to a laptop or desktop computer with a webcam.

Exclusion criteria

1. Insufficient knowledge of the English language.
2. Pregnancy or suspected pregnancy.
3. Current significant or unstable medical or psychiatric disorder needing acute treatment in its own right.
4. A lifetime diagnosis of substance dependence, psychosis, bipolar disorder, or borderline personality disorder.

5. Developmental or neurological disorder (e.g., dementia, attention deficit hyperactivity disorder, autism spectrum disorder).
6. Psychotropic medication other than a stable dosage of an antidepressant (e.g., selective serotonin reuptake inhibitor) for at least 14 days prior to study enrolment.
7. Non-removable metal parts in the area of the head (excluding dental work).
8. History of epilepsy or migraine.
9. Use of a pacemaker.

We will report the number of participants excluded, with reasons, and the number who decline consent or withdraw from the study, with reasons where provided.

Sample size

As TANDEM aims to establish feasibility rather than between-group differences, an a priori sample size calculation is not necessary. Guidance suggests that, where available, sample size should be based on previous feasibility or pilot studies of a similar intervention, or with a similar primary outcome measure or trial design. Where this information is lacking, it is argued that a total sample between $n = 12$ and $n = 50$ is sufficient for robust assessment of feasibility outcomes (39). Previous comparable trials in BED included 20 participants in each trial arm [e.g., (31, 41)]. As this trial includes four arms, we have chosen a target end study sample size of $n = 80$. Assuming the attrition to follow-up rate is ∼10% [as found in previous recent BED treatment trials, e.g., (42)], we will recruit an actual sample size of 88 (22 participants/group).

Randomization

The study will use a randomized controlled design, stratified by age, gender and BMI. Participants will be randomly allocated to a study group in a 1:1:1:1 ratio. Randomization will be completed using the Sealed Envelope Simple+ randomization service (https://www.sealedenvelope.com/). After completing the T2 assessment, participants in the waiting control arm will be offered ABMT.

Blinding and protection against bias

For pragmatic reasons, single-blinding will be implemented for [ABMT + real tDCS] and [ABMT + sham tDCS] groups. As such, participants in tDCS treatment groups will be blinded to real/sham allocation, but the researcher who leads treatment and conducts assessments will be unblinded. A validated protocol for sham stimulation will be used to deliver sham treatment; in the sham condition, tDCS electrodes will be properly mounted over the right and left dlPFC, and a 2mA current will be applied for 60 s at the beginning and end of each session. During the first and final 60 s of each session, no ABMT will be completed. Therefore, participants who receive sham will perceive typical sensations of tDCS (e.g., tingling), but will be unaffected by the stimulation. To assess if blinding was successful, participants will be asked to guess which condition they believe they have received and indicate how certain they feel about this. Once T2 and, where relevant the optional semi-structured interview about the treatment experience, are complete, participants will be unblinded. Those who receive sham treatment will not be offered any additional treatment. Blinding will not be implemented for ABMT only and waiting conditions.

The single-blind study design increases risk for experimenter bias. To protect against bias, self-report questionnaires (as opposed to interviews) will be used to assess clinical outcomes, including episodes of binge eating. All outcome measures will be collected online using either Qualtrics^{XM} for questionnaire measures, or Gorilla^{TM} or Inquisit Millisecond for neurocognitive task measures. As such, the experimenter will have no influence on participant responding or task performance. Semi-structured interviews about the treatment experience will be conducted before participants are unblinded and by independent investigators who are naïve to real/sham allocation.

Intervention

Participants will complete 10 sessions of tele-supervised treatment over 2–3 weeks (i.e., week daily sessions until 10 sessions have been completed). Sessions will involve either concurrent ABMT and real/sham tDCS, or ABMT only. Participants in the waiting control arm will receive ABMT after completion of the T2 assessment.

Attention bias modification training

ABMT aims to train participants to "look toward" low-calorie food and "look away" from high-calorie food using a modified version of the anti-saccade task by Werthmann et al. (43). Training is completed on a personal laptop or desktop computer and lasts 10–15 min with breaks. Participants completing concurrent treatment (i.e., ABMT + real/sham tDCS) will begin ABMT 5 min after starting the stimulation. They will also be instructed to rest while waiting to begin and after completing the training.

ABMT paradigm

The modified task consists of 360 trials. Of these, 180 require participants to look toward low calorie foods, and 180 trials require participants to look away from high calorie foods. At the beginning of each trial, a black fixation point appears for 100 ms, followed by a red or blue fixation point (500 ms). A blue point

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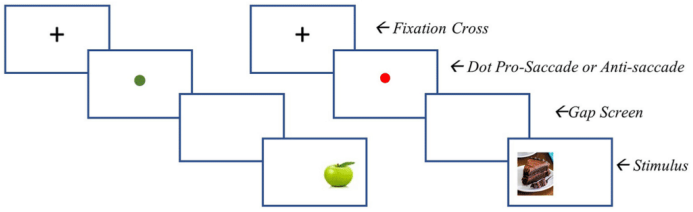

FIGURE 1
ABMT stimulus presentation. Left = pro-saccade stimulus presentation (i.e., participant is to look toward the food image presented). Right = anti-saccade stimulus presentation (i.e., participant is to move their gaze away from the stimulus).

indicates that a pro-saccadic eye movement is required (i.e., look toward the food picture which appears after the fixation point), whereas a red point requires an anti-saccadic eye movement (i.e., direct the gaze away from the food picture which appears after the fixation point). Low-calorie cues are always preceded by a blue dot and high calorie food cues are always preceded by a red dot. A blank screen is inserted for 200 ms between the fixation point and the stimulus presentation. The pictorial stimulus (a high- or low-calorie food picture) then appears on either the left or the right side of the screen for 500 ms. Inter-trial interval is 1,300 ms. Trials will be presented in a random order across three blocks, each including 120 trials. See Figure 1 for an example of a pro-saccade and anti-saccade stimulus presentation.

Stimuli

Pictorial stimuli are 30 low calorie food and 30 high calorie food pictures, which are visually matched for brightness, color, and complexity, taken from Werthmann et al. (43). Each image is presented twice in each block, once on the left side of the screen and once on the right side of the screen (in a counterbalanced order), resulting in a total of 360 training trials (30 food stimuli + 30 non-food stimuli × 2 positions × 3 blocks).

Response and feedback

In addition to directing their gaze toward or away from the stimulus presented, participants will be instructed to press the arrow key which corresponds with the direction of their gaze. Response latencies will be recorded to monitor accuracy and provide participants with feedback. For each block, the number correct responses will be summed up and presented as percentage score of correct performance to the participant.

Self-administered transcranial direct current stimulation

Participant administered tDCS will be delivered using the Newronika HDC system (Figure 2). The Newronika system

FIGURE 2
Equipment for TDCS self-administration.

consists of an easy to use, lay friendly stimulator, a programming device used by the researcher to securely set stimulation parameters, and a customisable MindCap electrode placement system which ensures simple, safe, and reliable placement of the anode and cathode over the right and left dlPFC. Stimulation will be delivered at a constant current of 2 mA (with a 30 second fade in/fade out) for 20 min. This tDCS montage has been used in studies of food craving, bulimia nervosa, and BED (28, 32, 41, 44). As with real tDCS, sham stimulation will run for 20 min however, participants will not receive active stimulation for the full 20-min period. Instead, sham participants will receive 60 s of stimulation at the start ("ramping up") and the end ("ramping down") of the stimulation period.

Rationale for session number and frequency

Although consensus around the optimal number of ABMT sessions is lacking, a review of meta-analyses of CBM concluded that the number of sessions appears to moderate outcomes, with higher session numbers being associated with greater change in cognitive bias (18). In line with this, Beard, Sawyer et al. (45) found that as session number increased, so did the potency of

the effect of CBM on symptoms in depression, anxiety, and addiction disorders. However, this effect appeared to stabilize after 10 sessions. Therefore, 10 sessions may be the optimal dose for ABMT.

With regards to tDCS, although there is a similar lack of consensus about the optimal treatment parameters, it is broadly accepted that multiple sessions are needed to achieve lasting therapeutic effects (27, 44). The vast majority of multisession studies in psychiatric disorders have applied 10-sessions of tDCS once daily over 2–3 weeks (27). Thus, the choice of 10 sessions is also supported by the literature on tDCS use in psychiatric disorders.

Safety procedures

Published guidance for ensuring participant safety during self-administration of tDCS will be adhered to Knotkova et al. (46). This guidance is as follows: First, training and supervision should be provided to those self-administering tDCS. In TANDEM, all participants will be trained in safe tDCS self-administration, and all treatment sessions will be supervised *via* video-call. Second, the tDCS equipment used must be intended for home use by the lay community. We will use the Newronika HDC stimulator and MindCap electrode placement system which is CE marked for supervised home use in the UK and Europe. This equipment is pre-programmed by the researcher, simple to use, and includes features which prevent misuse (e.g., the researcher can set a minimum time between treatment sessions, and/or set a maximum number of sessions before re-calibration by the researcher). Third, care must be given to the participant's capacity for self-administration. Prior to beginning treatment, the TANDEM researcher will assess each participant's ability to self-administer tDCS safely. Where necessary, additional training will be provided. Participants who cannot safely self-administer tDCS after training will be withdrawn from the study, and the reason for their withdrawal will be reported. Fourth, tDCS tolerance and adverse events must be assessed at each session. Consistently, process outcomes will monitor tDCS tolerance and adverse events at each treatment session (see "Outcome Assessment" for more details), In addition, during or near to the final (T2) assessment, tDCS tolerance and adverse events will be assessed in an optional semi-structured interview about the treatment experience.

Concomitant care

As the trial focusses on feasibility rather than efficacy, participants will be allowed to receive other parallel treatments for their ED. Concurrent use of psychoactive medications (excluding neuroleptics or benzodiazepines) will be allowed, providing the dose has been stable for at least 14 days prior to baseline assessment.

Trial procedure

The individual participant timeline is illustrated in Figure 3. Study duration for each participant is 8 weeks. All participants will partake in assessments at each of the three time points; baseline (T0), post-treatment (T1) and follow-up (T2). Each assessment will be completed *via* videoconferencing (i.e., participants complete both assessments and treatment at home using a laptop or desktop computer with a webcam). Questionnaire measures will be completed online using Qualtrics^{XM} and neurocognitive tasks will be completed online using either Gorilla^{TM} or Millisecond by Inquisit^{TM}.

Informed consent will be provided *via* an online consent form (Qualtrics^{XM}). Once completed, potential participants will be screened over the phone for inclusion in the study. At screening, BED diagnosis is confirmed using a standardized interview [Eating Disorders Diagnostic Screen; (47)]. Physical and psychiatric comorbidities, current medications, and tDCS safety are assessed using a general health questionnaire developed for the purpose of screening. Eligible participants then complete the baseline (T0) assessment. After baseline assessment, participants are randomized to one of four groups: (1) ABMT + real tDCS, (2) ABMT + sham tDCS, (3) ABMT only, or (4) wait-list control group. Intervention groups will then complete 10 sessions of treatment, up to 5 sessions/week, across 2–3 weeks. The waitlist control group will receive no experimental treatment during this time. All participants will complete the post-treatment assessment (T1) after the 10th (final) session of treatment or 2-weeks of waiting, and the follow-up assessment (T2) 6-weeks after completing treatment, or after 8-weeks of waiting. After completing the final (T2) follow-up, waiting control participants will receive ABMT.

Outcome assessment

Primary outcomes

The primary clinical outcome will be monthly episodes of binge eating, as measured by the Eating Disorders Examination Questionnaire [EDE-Q; i.e., change in the number of monthly episodes of binge eating from baseline (T0) to follow-up (T2)]. Medians and rate ratios (with confidence intervals) will be reported, and these will inform the minimum sample size required for a fully powered large-scale RCT. Rates for recruitment and retention to 8-week follow up will also be reported to provide insight into the time and resources needed for a larger trial.

Intervention acceptability will be assessed in two ways. First, by asking participants the following two questions at post treatment (T1) and follow-up (T2) assessments: (1) "If you could continue with this treatment, would you?" (Yes/No) and "Would you recommend this treatment to a friend who was struggling with binge eating?" (Yes/No). The intervention

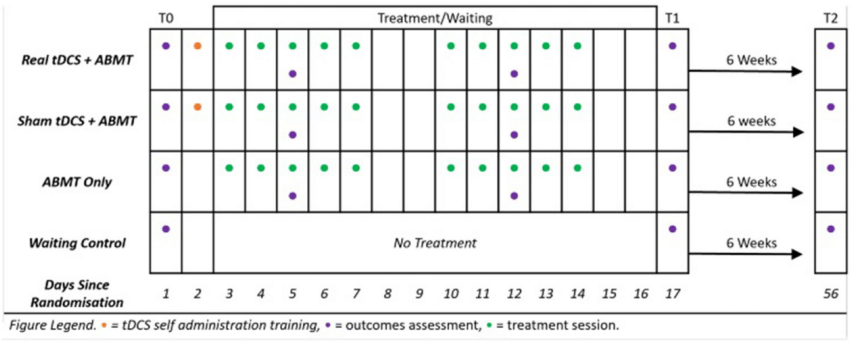

FIGURE 3
TANDEM participant timeline.

will be viewed as acceptable if at least 75% of those who receive the real concurrent treatment indicate that they would continue the intervention if given the opportunity and/or if 75% would recommend the treatment to a friend. Second, at or near-to the final (T2) assessment, participants will be invited to complete an optional semi-structured interview about the treatment experience. This will provide qualitative data which will give insight into (a) whether participants viewed the treatment as acceptable and (b) why/why not. Interviews will be recorded, transcribed, and analyzed using thematic analysis.

Feasibility will also be assessed by looking at participant ratings of tDCS tolerability. Participants who receive tDCS will complete a 10-point visual analog scale (VAS) of tDCS discomfort after each session. We will then take the average of ratings across the ten sessions for each participant and use this to assess the average rating for tDCS related discomfort for the real tDCS + ABMT group. The intervention will be considered well-tolerated if this number is $\leq$4 (i.e., mild discomfort). Prior to beginning each tDCS session, participants will also report any side effects they have experienced since their previous session. The type and frequency of side effects will be reported for consideration.

Secondary outcomes

Secondary outcomes will be assessed using validated self-report instruments and neuropsychological tasks. Change in score/performance from baseline (T0), to post treatment (T1) and follow up (T2) will be examined by looking at within and between group effect sizes and standard deviations. These data will inform outcome measure selection for a future large-scale RCT.

Outcome measures

See Table 1 for a summary of the measures collected at each timepoint.

Questionnaires measures

Participants will complete a battery of questionnaire measures at each assessment (T0, T1 and T2). These will assess ED psychopathology [Eating Disorder Examination Questionnaire (48)], general psychopathology [Depression, Anxiety and Stress Scale – 21 item version (49)], craving for food [Food Craving Questionnaire – trait version (50)], ED related clinical impairment [Clinical Impairment Assessment (51)], emotion regulation [Difficulties with Emotion Regulation Scale – 16 item version (52)], and impulsivity [Barratt Impulsiveness Scale (53)]. Self-reported weight and height will be used to calculate BMI.

Task measures of neurocognition

Attention bias toward high calorie foods will be assessed using the visual probe task described in Mercado et al. (54). In TANDEM, as participants will be taking part from home, webcam based eye-tracking technology (as opposed to specialist

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TABLE 1 Summary of outcome assessment by visit.

	Screening	T0	During treatment	T1	T2
Eating disorder diagnostic screen	X				
TDCS safety screen	X				
General health and lifestyle questionnaire	X				
Demographics		X			
Eating disorder examination questionnaire (EDE-Q)		X		X	X
Depression, anxiety, stress scale (DASS-21)		X		X	X
Food craving questionnaire—trait version		X		X	X
Clinical impairment assessment (CIA)		X		X	X
Difficulties in emotion regulation scale (DERS)		X		X	X
Barrett impulsiveness scale (BIS-11)		X		X	X
Visual probe task		X		X	X
Food attention network task		X		X	X
N-back task		X		X	
Wisconsin card sorting task		X		X	
Delay discounting task		X		X	
Affective go/no go task		X		X	
VAS measures		X	X	X	X
Assessment of tDCS discomfort/Side effects			X		
Semi-structured interview about treatment (optional)					X

lab-based eye-tracking equipment) will be used to record eye movements.

Food-related attention will be assessed using the food-specific attention network task described in Heve, Stingl et al. (55) and in Mercado et al. (54). This task examines three components of attention (alerting, orienting, and executive function) using food (low- and high-calorie) and non-food picture stimuli.

Working memory will be assessed using the n-back task described in Meiron and Lavirdor (56). Accuracy (% correct responses) and reaction time for correct responses (ms) will be reported.

Affective inhibitory control will be assessed using the Face Affective Go/No Go task from the EMOTICOM neuropsychological test battery (57). Error rate and latency will be used to estimate inhibitory control, and reaction times will be used to calculate affective bias scores.

Cognitive flexibility will be assessed using the Wisconsin Card Sorting Test (58). Difficulties with set-shifting will be reflected in perseverative errors, thus, higher scores on this test indicate poorer performance.

Preference for immediate vs. delayed rewards will be assessed using the delay discounting task described by Kirby and Maraković (59). Modeling techniques are used to fit participant responses to the function that relates time to discounting. This produces a temporal discounting curve. The rate at which delayed rewards are discounted will be derived by calculating the area under the curve, and steeper discounting will be reflected by a smaller area under the curve (60).

Optional semi-structured interview

All participants (i.e., including those who received ABMT only) will be invited to complete a semi-structured interview about the treatment experience. This interview, developed for the TANDEM trial, was based on previous semi-structured interviews about tDCS treatment by Gordon et al. (33) and Smits et al. (61). Questions examined seven domains of acceptability: affective attitudes, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness, and self-efficacy. Interview prompts are included in the Supplementary material.

Within session measures

At each treatment session, participants will complete measures of current symptoms and, where relevant, tDCS related discomfort. Before each treatment begins, participants will complete an online "check in" questionnaire which asks about episodes of binge eating since their previous session and, where relevant, adverse events/side effects that may be related to tDCS. They then complete 10-point visual analog scales (VAS) assessing current hunger, feeling of fullness, craving for food, urge to binge, level of tension, level of stress, level of discomfort, and feeling of low mood. At the end of each session, participants complete a "check-out" questionnaire which repeats

VAS measures and, where relevant, asks about tDCS related discomfort during the session.

Data analysis

The primary analysis will use the number of episodes of binge eating in a Poisson regression model with baseline adjustment. Descriptive statistics will be used to assess recruitment and retention rates, intervention adherence, and the quality and completeness of the data. In secondary analyses, a mixed model approach will be used to analyse the effect of treatment on primary (PO) and secondary outcomes (SOs), with baseline adjustment. To examine the whether the effect of treatment is different for different levels of overweight or obesity, BMI will be included in the model as an interaction effect. Effect sizes will be analyzed and reported for PO and SOs. For the Poisson regression, rate ratios will be reported. For binary outcomes, odds ratios will be reported. For quantitative outcomes, standardized differences will be reported. Primary parameters will be time vs. treatment interactions at both timepoints after baseline. *P*-values will be reported but for exploratory purposes only (i.e., they will not be interpreted to accept or reject the null hypothesis). The analyses will be done in the intent to treat population, which is defined by including all patients with baseline assessment. Outcome data already obtained for participants who discontinue or deviate from the intervention protocol will be kept and analyzed. Analyses will be conducted using RStudio (62).

Patient and public involvement

In our previous trial of tDCS enhanced CBM in BED, a subset of participants completed a semi-structured interview about their treatment experience (33). These interviews included a question about participant views about future directions for tDCS in BED. While these responses did not refer directly to at-home treatment, participants described practical barriers to accessing treatment (e.g., caring responsibilities, time pressures, and travel burden). From these responses, we inferred that participants would welcome investigation into at-home treatment. Prior to submitting the study protocol for review by the research ethics committee, 10 randomly selected participants from our previous trial were invited to provide feedback about the proposed intervention procedures, and the objectives for the research. Eight participants responded with constructive feedback which was incorporated into the study before ethics approval was awarded.

Participant facing forms were also reviewed by people with lived experience of mental health problems and their carers *via* the South London and Maudsley's Feasibility and Acceptability Support Team for Researchers (FAST-R).

Ethical considerations

The TANDEM trial was awarded favorable opinion by the London-Fulham NHS Research Ethics Committee on the 6th of August 2020 (REC Reference 20/LO/0936). Approval to begin the trial was granted by the Health Research Authority (HRA) on the 6th of August 2020. All trial participants will provide written informed consent prior to inclusion into the study and may withdraw from the trial at any point, without consequence or giving a reason.

Discussion

The TANDEM trial will be among the first feasibility studies of concurrent tDCS with cognitive training in BED [see also (33, 41)]. As such, we expect it will contribute new information and will inform the continued development of neurobiologically informed approaches to BED treatment. Indeed, should this trial evidence that concurrent tDCS and ABMT is feasible and acceptable, a large-scale trial with long-term follow up will be needed to evaluate treatment effectiveness.

The design has several strengths. While most studies of tDCS use convenience samples from healthy populations, TANDEM will use a clinical sample who meet DSM-5 criteria for BED. Second, by bringing brain-based treatment into the home, TANDEM overcomes a number of barriers to treatment cited by participants in previous studies (33, 63). Moreover, we will increase access to treatment during a time of elevated uncertainty and compromised access to conventional care (i.e., during the coronavirus pandemic). In fact, in a letter to Brain Stimulation, Caulfield and George (2020) called for this type of approach, saying that the time is ripe for investigating at home neurotherapeutics, and that tDCS is a prime candidate (64). Third, we have tested our CBM intervention (ABMT) in trials involving adults with obesity (54) and anorexia nervosa: in this latter case, training focused on altering avoidance of food, as opposed to bias toward high-calorie foods (65). As such, we have a useful preliminary understanding of the therapeutic effects of ABMT in populations with EDs and disordered eating behaviors, and a good understanding of how participants view the treatment (i.e., acceptable, accessible, and credible). Fourth, we have chosen a primary outcome with high clinical relevance (i.e., monthly episodes of binge eating), and, unlike many studies which examine short-term intervention effects, we have incorporated a comparatively long follow up period (6-weeks post treatment end). This will allow us to examine the maintenance of any therapeutic effects observed immediately post treatment and allow time for more gradual changes to emerge.

There are some challenges for the TANDEM trial. TANDEM is/has been conducted during the coronavirus pandemic (COVID-19) and it is possible that there may be a negative

COVID-related impact on recruitment and retention. In response, TANDEM has adopted a fully remote design (i.e., participants complete all components of treatment and research participation from home). We expect that this may mitigate the negative impact of COVID on recruitment however, by adopting a fully remote design, TANDEM has sacrificed some of the advantages of conducting research in the lab (e.g., access to state-of-the art eye tracking equipment, controlled testing environments, and reduced reliance on self-report data). In publications arising from this trial, we will comment on the quality and completeness of the data collected to assist with future decisions about trial design. Finally, to minimize attrition, we have chosen to collect only a subset of outcome measures at 8-week follow up. As such, we will not be able to comment on change from baseline to follow up for some secondary neurocognitive outcomes.

We expect that the TANDEM trial will provide a valuable contribution to the literature on concurrent tDCS and CBM treatments for EDs, and that the data collected will provide a foundation for future related trials. Moreover, we hope that TANDEM will shed light on the potential for bringing NIBS treatments into the home so that we can continue increasing access to novel treatments for psychiatric disorders.

Trial progress

Recruitment commenced in March 2021 and ended in February 2022. Data collection will be completed by June 2022. Amendments to the study protocol will be reported in publications of study outcomes.

Author contributions

MF, IC, and US conceived the idea for the trial. MF led trial design and obtained ethical approvals. The manuscript was written by MF with input/feedback from IC and US. All authors contributed to the article and approved the submitted version.

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Acknowledgments

Thank you to all participants in the TANDEM cohort for helping us in our research.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.949246/full#supplementary-material

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Appendix C. Ethical approval letters and documents

Appendix C.1. Favourable opinion letter London-Fulham Research Ethics Committee

NHS
Health Research Authority

London - Fulham Research Ethics Committee
Barlow House
3rd Floor, 4 Minshull Street
Manchester
M1 3DZ

Please note: This is an acknowledgement letter from the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

06 August 2020

Ms Michaela Flynn
PO59
16 De Crispigny Park
London
SE58AF

Dear Ms Flynn

Study title:	**A feasibility study of neuromodulation with attention bias modification training for binge eating disorder**
REC reference:	**20/LO/0936**
Protocol number:	**N/A**
IRAS project ID:	**284609**

Thank you for your letter of 04 August 2020. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 28 July 2020

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Cover Letter [Response to REC]		04 August 2020

Participant consent form [TANDEM Consent Form]	4	30 July 2020
Participant consent form [TANDEM Interview Consent Form]	4	30 July 2020
Participant information sheet (PIS) [TANDEM PIS]	4	30 July 2020
Participant information sheet (PIS) [TANDEM Interview PIS]	4	30 July 2020
Research protocol or project proposal [TANDEM Protocol]	2	30 July 2020

Approved documents

The final list of approved documentation for the study is therefore as follows:

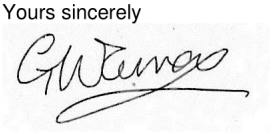
Document	*Version*	*Date*
Copies of advertisement materials for research participants [TANDEM Poster]	3	10 June 2020
Copies of advertisement materials for research participants [TANDEM Poster]	3	10 June 2020
Copies of advertisement materials for research participants [TANDEM Poster]	3	10 June 2020
Copies of advertisement materials for research participants [TANDEM Online Advertisement Test]	1	08 June 2020
Cover Letter [Response to REC]		04 August 2020
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Evidence of KCL Insurance]		23 July 2019
GP/consultant information sheets or letters [Letter to GP/Clinician]	1	17 April 2020
Interview schedules or topic guides for participants [TANDEM Interview Topic Guide]	1	17 May 2020
IRAS Application Form [IRAS_Form_25062020]		25 June 2020
Letter from funder [Evidence of funding via KCL Postgraduate Research Studentship]		26 November 2019
Letter from sponsor [Confirmation of sponsorship]		24 June 2020
Non-validated questionnaire [VAS]	1	17 May 2020
Non-validated questionnaire [tDCS Safety Screen]	1	16 May 2020
Non-validated questionnaire [Demographics]	1	16 May 2020
Non-validated questionnaire [tDCS Self-Administration Checklist]	1	16 May 2020
Non-validated questionnaire [Core Symptom Assessment]	1	18 September 2019
Non-validated questionnaire [Psychopathology Symptom Assessment]	1	18 September 2019
Other [Evidence of KCL insurance]	1	24 May 2019
Other [Evidence of Permission to use Intake24]	1	09 June 2020
Other [Confirmation of Studies letter for Michaela Flynn]	1	29 May 2020
Other [Good Clinical Practice Certificate for Michaela Flynn]	1	05 June 2020
Other [Evidence of PPI]	1	25 May 2020
Other [Evidence of PPI]	1	16 May 2020
Other [Terms of reference for TSC/DMC]	1	09 June 2020
Other [Quote for Courier Service]	1	09 June 2020
Other [Due Diligence form]	1	08 June 2020
Other [Participant Equipment Return Agreement]	1	08 June 2020

Participant consent form [TANDEM Consent Form]	4	30 July 2020
Participant consent form [TANDEM Interview Consent Form]	4	30 July 2020
Participant information sheet (PIS) [TANDEM PIS]	4	30 July 2020
Participant information sheet (PIS) [TANDEM Interview PIS]	4	30 July 2020
Referee's report or other scientific critique report [Evidence of Peer Review]		24 May 2020
Referee's report or other scientific critique report [Evidence of Peer Review]		18 May 2020
Research protocol or project proposal [TANDEM Protocol]	2	30 July 2020
Summary CV for Chief Investigator (CI) [CV for PI]		24 June 2020
Summary CV for student [CV for Michaela Flynn]		24 June 2020
Summary CV for supervisor (student research) [CV for Iain Campbell]		24 June 2020
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Participant Facing Summary of the Participation Procedure]	1	27 May 2020
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Participant Facing Summary of the Treatment Procedure]	1	27 May 2020
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Flow Diagram Summary of Study Protocol]	1	24 June 2020
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Schematic summary of the intervention protocol for professional audience]	1	24 June 2020
Validated questionnaire [EDDS]		
Validated questionnaire [EDE-Q]		
Validated questionnaire [DASS-21]		
Validated questionnaire [FCQ]		
Validated questionnaire [ERQ]		
Validated questionnaire [PFS]		
Validated questionnaire [YFAS]		
Validated questionnaire [CIA]		
Validated questionnaire [PANAS]		
Validated questionnaire [BIS-11]		
Validated questionnaire [DGI]		

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

IRAS Project ID: 284609	Please quote this number on all correspondence

Yours sincerely



Gemma Warren
Approvals Specialist

E-mail: fulham.rec@hra.nhs.uk

Copy to: Ms Michaela Flynn

Lead Nation
England: approvals@hra.nhs.uk

Appendix C.2. Approval letter from the Health Research Authority

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Ulrike Schmidt
PhD Supervisor
King's College London
Department of Psychological Medicine
Section of Eating Disorders
IoPPN, P059
SE5 8AZ

Email: approvals@hra.nhs.uk

06 August 2020

Dear Professor Schmidt

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**A feasibility study of neuromodulation with attention bias modification training for binge eating disorder**
IRAS project ID:	**284609**
Protocol number:	**N/A**
REC reference:	**20/LO/0936**
Sponsor	**King's College London**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **284609**. Please quote this on all correspondence.

Yours sincerely,
Gemma Warren

Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: *Prof Reza Razavi*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Copies of advertisement materials for research participants [TANDEM Poster]	3	10 June 2020
Copies of advertisement materials for research participants [TANDEM Poster]	3	10 June 2020
Copies of advertisement materials for research participants [TANDEM Poster]	3	10 June 2020
Copies of advertisement materials for research participants [TANDEM Online Advertisement Test]	1	08 June 2020
Cover Letter [Response to REC]		04 August 2020
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Evidence of KCL Insurance]		23 July 2019
GP/consultant information sheets or letters [Letter to GP/Clinician]	1	17 April 2020
Interview schedules or topic guides for participants [TANDEM Interview Topic Guide]	1	17 May 2020
IRAS Application Form [IRAS_Form_25062020]		25 June 2020
Letter from funder [Evidence of funding via KCL Postgraduate Research Studentship]		26 November 2019
Letter from sponsor [Confirmation of sponsorship]		24 June 2020
Non-validated questionnaire [Demographics]	1	16 May 2020
Non-validated questionnaire [tDCS Self-Administration Checklist]	1	16 May 2020
Non-validated questionnaire [Core Symptom Assessment]	1	18 September 2019
Non-validated questionnaire [Psychopathology Symptom Assessment]	1	18 September 2019
Non-validated questionnaire [VAS]	1	17 May 2020
Non-validated questionnaire [tDCS Safety Screen]	1	16 May 2020
Other [Evidence of KCL insurance]	1	24 May 2019
Other [Evidence of Permission to use Intake24]	1	09 June 2020
Other [Confirmation of Studies letter for Michaela Flynn]	1	29 May 2020
Other [Good Clinical Practice Certificate for Michaela Flynn]	1	05 June 2020
Other [Evidence of PPI]	1	25 May 2020
Other [Evidence of PPI]	1	16 May 2020
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Validated questionnaire [EDE-Q]		
Validated questionnaire [DASS-21]		
Validated questionnaire [FCQ]		
Validated questionnaire [ERQ]		
Validated questionnaire [PFS]		
Validated questionnaire [YFAS]		
Validated questionnaire [CIA]		
Validated questionnaire [PANAS]		
Validated questionnaire [BIS-11]		
Validated questionnaire [DGI]		

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
The single participating NHS organisation will act as a PIC.	This is a single site study co-sponsored by the participating NHS organisation. You should work with your sponsor R&D office to make arrangements to set up the study. The sponsor R&D office will confirm to you when the study can start following issue of HRA and HCRW Approval.	This is a single site study co-sponsored by the participating NHS organisation therefore no agreements are expected.	The study is funded by the King's College London Post Graduate Research International Student Scholarship.	The single participating NHS organisation will act as a PIC and therefore, a Local Collaborator or Principal Investigator is not expected for the study.	The single participating NHS organisation will act as a PIC and therefore, HR good practice arrangements are not expected for the trial.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

Appendix C.3. Amendment approval letter from the Health Research Authority

NHS
Health Research Authority

London - Fulham Research Ethics Committee

Barlow House
3rd Floor, 4 Minshull Street
Manchester
M1 3DZ

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

18 November 2020 (Re-issue 20th November 2020)

Ms Michaela Flynn
PO59
16 De Crispigny Park
London
SE58AF

Dear Ms Flynn

Study title:	**A feasibility study of neuromodulation with attention bias modification training for binge eating disorder**
REC reference:	**20/LO/0936**
Protocol number:	**N/A**
Amendment number:	**SA 01**
Amendment date:	**24.09.20**
IRAS project ID:	**284609**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Completed Amendment Tool [TANDEM Amendment Tool-Locked.pdf]	SA 01	29 September 2020
Copies of advertisement materials for research participants [TANDEM Poster]	4	09 September 2020
Copies of advertisement materials for research participants [TANDEM Website Advertising Text]	2	09 September 2020
Copies of advertisement materials for research participants [TANDEM Facebook Advertisement]	4	09 September 2020
Covering letter on headed paper [Cover Letter]	1	09 September 2020
GP/consultant information sheets or letters [TANDEM Notice for GPs and Clinicians]	2	09 September 2020
Participant consent form [TANDEM Consent Form]	5	09 September 2020
Participant information sheet (PIS) [TANDEM PIS]	6	05 November 2020
Research protocol or project proposal [TANDEM Protocol]	3	09 September 2020

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Amendments related to COVID-19

We will update your research summary for the above study on the research summaries section of our website. During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you have not already done so, please register your study on a public registry as soon as possible and provide the HRA with the registration detail, which will be posted alongside other information relating to your project.

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.

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS Project ID - 284609:	**Please quote this number on all correspondence**

Yours sincerely

pp
Chair

E-mail: fulham.rec@hra.nhs.uk

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Ms Michaela Flynn*

London - Fulham Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 07 October 2020

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr Keith Berelowitz (Vice Chair)	Director of Operations Richmond Pharmacology	Yes	
Dr Jan Downer	Consultant Anaesthetist	Yes	
Mrs Deborah Morgan	Clinical Project Manager	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Dr Keith Haylock	Approvals Administrator
Mr David Parr	Approvals Officer

Appendix C.4. King's College London Data Protection Office letter of registration

Research Governance Office

Franklin Wilkins Building
4.19 Waterloo Bridge Wing
Waterloo Road
London SE1 9NH
Telephone 020 7848 1239/3323
rgo@kcl.ac.uk

26/08/2020

Michaela Flynn

Dear Michaela

KDPR Registration Reference: DPRF-19/20-15934
Project Title: TANDEM

Thank you for submitting the above Research Data Protection Registration Form. This letter acknowledges confirmation of your registration; your registration confirmation reference number is detailed above.

Be sure to keep a record your registration number. A copy of this letter will automatically be stored in your KDPR account, but you may wish to keep a separate copy in your own records.

Registration is valid for the data holding period you have indicated within the form.

Please note it is the responsibility of the researcher to ensure that any other permissions or approvals (i.e. Research Ethics, R&D, gatekeepers, etc.) relevant to their research are in place, prior to data collection.

Modifications

Should there be any changes to the conduct of your study or your study timelines which will impact on how you collect, manage or otherwise use your data, then you must submit a modification request in KDPR, indicating what has changed. Modification requests will be required in instances such as (this is not an exhaustive list):

- Change of storage repository
- Change to data retention period
- Change of data controller if that person should leave the College
- Change to the nature of the identifiers in the data you collect
- Change of anticipated start date of data collection

You will find the modification request form within the project you have created. You can access this by selected 'Create sub-form' in the left hand tiles on the screen and selecting 'Modification Request Form.'

Audit:

As part of the College's responsibilities under the General Data Protection Regulation, it must ensure that data is collected, managed and otherwise used as outlined within the submitted registration forms. As such the College is required to audit this process. You may therefore be selected for a random audit, to see how researchers are implementing this process. If audited, you will be expected to provide evidence that you are collecting, managing or otherwise using your data as outlined within the form.

If you have any questions regarding your registration please email rgo@kcl.ac.uk

We wish you every success with your project.

With best wishes

KCL Research Governance Office

Appendix C.5. Letter of Access to South London and Maudsley NHS Foundation Trust

Research and Development Office

Box P005
De Crespigny Park
Denmark Hill
London SE5 8AF
Tel +44 (0)20 7848 0790

Ms Michaela Flynn

Institute of Psychiatry Psychology and Neuroscience
King's College London
De Crespigny Park
London SE5 8AF

18th August 2020

Dear Michaela,

Letter of access for research

In accepting this letter, the participating organisation confirms your right of access to conduct research through their organisation for the purpose and on the terms and conditions set out below. This right of access commences on **18/08/2020** and ends on **30/12/2021** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from South London and Maudsley NHS Foundation Trust. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving confirmation from the individual organisation (s) of their agreement to conduct the research.

The information supplied about your role in research in South London and Maudsley NHS Foundation Trust has been reviewed and you do not require an honorary research contract with the organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out. Evidence of checks should be available on request to the organisation.

You are considered to be a legal visitor to the South London and Maudsley NHS Foundation Trust premises. You are not entitled to any form of payment or access to other benefits provided by the organisation or this organisation to employees and this letter does not give rise to any other relationship between you and the organisation, in particular that of an employee.

While undertaking research through South London and Maudsley NHS Foundation Trust you will remain accountable to your employer **King's College London**, but you are required to follow the reasonable instructions of your nominated manager **Prof Ulrike Schmidt** in SLaM or those given on her behalf in relation to the terms of this right of access.

Where any third-party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any

investigation by South London and Maudsley NHS Foundation Trust in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.
You must act in accordance with the organisations policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with the South London and Maudsley NHS Foundation Trust in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on the organisations premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of a contract holder and you must act appropriately, responsibly and professionally at all times.

If you have a physical or mental health condition or disability which may affect your research role, and which might require special adjustments to your role, if you have not already done so, you must notify your employer and each organisation prior to commencing your research role at that organisation.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and the Data Protection Act 2018. Furthermore, you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times or are able to prove your identity if challenged. Please note that the South London and Maudsley NHS Foundation Trust does not accept responsibility for damage to or loss of personal property.

South London and Maudsley NHS Foundation Trust may revoke this letter and any organisation(s) may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of South London and Maudsley NHS Foundation Trust or if you are convicted of any criminal offence. You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children, this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you MUST stop undertaking any regulated activity immediately.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

No organisation will indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 2018. Any breach of the Data Protection Act 2018 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in South London and Maudsley NHS Foundation Trust and the SLaM/IoPPN R&D office.

Yours sincerely,

Tereza Cepelkova
Research Governance Facilitator
Joint R&D Office of South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology & Neuroscience

cc: HR Department of the substantive employer

Appendix C.6. Approval letter from the King's College London Research Ethics Committee

Research Ethics Office

Franklin Wilkins Building
5.9 Waterloo Bridge Wing
Waterloo Road
London SE1 9NH
Telephone 020 7848 4020/4070/4077
rec@kcl.ac.uk

KING'S College LONDON

Michaela Flynn

2 November 2020

Dear Michaela

Reference Number: LRS-19/20-20873

Study Title: Cognitive Control Functions in Binge Eating Disorder and Obesity (CoCo)

Review Outcome: Further amendments/clarifications required before approval can be granted.

Thank you for submitting the above application for ethical approval. Your application has been reviewed and has been approved pending amendments. You are now required to address a number of issues before full approval is granted. These are specified in the feedback table below. Please respond to each point raised by the reviewer and amend your application form, and appendices, accordingly. **Please note that research involving human participants must not commence until your amended application has been reviewed and Full Approval has been granted.**

In order to amend the application, you will simply need to log on onto REMAS and modify the existing application. Once again, your academic supervisor will be required to provide verification.

The submission of your amended application must be accompanied by a cover letter outlining the changes you have made in response to each of the Committee's requests. For ease of completion we recommend that you cut and paste the feedback table from your outcome letter into your cover letter and respond to each point individually. The cover letter should be attached as a Supporting Document in section I9 of your application. Failure to attach a cover letter to your resubmitted application will result in your application being marked as 'Invalid' and returned to you by the Research Ethics Office prior to review.

Please note, once submitted amendments will be reviewed within 15 working days.

If for some reason you choose not to proceed with this research ethics application, please inform the Research Ethics Office.

Yours sincerely,

The Research Ethics Office

For and on behalf of

PNM Research Ethics Panel

Cc: Prof Ulrike Schmidt

Major Issues (will require substantial consideration by the applicant before approval can be granted)

H7: Please consider if high-risk ethical review is required due to the potential to case participants' stress/anxiety. If you feel as though a high-risk review is not applicable, please outline your justification.

Minor Issues related to application (the reviewer should identify the relevant section number before each comment)

C4: Please clarify if ethical clearance for TANDEM participants is being requested, or if this has already been obtained from the HRA. If so, has the project been submitted to the HRA or has this been split between Committees?

Minor Issues related to recruitment documents

Consent Form

If data is being stored/ archived for future use (E9) please insert a point to allow participants to consent to this.

Adverts

Appendix C.7. Health Research Authority annual progress report

NHS
Health Research Authority

Annual Progress Report to Research Ethics Committee

For all studies except clinical trials of investigational medicinal products

To be completed and submitted by the Chief Investigator or sponsor. Please email this report to the REC. For questions with Yes/No options please indicate answer in bold type.

1. Details of the Chief Investigator

Name:	Professor Ulrike Schmidt
Address:	Dept. of Psychological Medicine, Section of Eating Disorders, IoPPN, PO-59, De Crespigny Park, London, SE5 8AF
Telephone:	020 7848 0181
E-mail:	Ulrike.schmidt@kcl.ac.uk

2. Details of study

Full title of study:	A feasibility study of neuromodulation with attention bias modification training for binge eating disorder
IRAS ID:	284609
Name of REC:	London - Fulham Research Ethics Committee
REC reference number:	20/LO/0936
Date of favourable ethical opinion:	06/08/2020
Sponsor:	King's College London, South London and Maudsley NHS Foundation Trust

Annual progress report (non-CTIMP), version 4.6, dated January 2021

3. Commencement and termination dates

Has the study started?	Yes
If yes, what was the actual start date?	01/02/2021
If no, what are the reasons for the study not commencing? What is the expected start date? Please note, if the study will not start within 24 months of the REC Favourable Opinion date the REC may review its' opinion.	
Has the study finished? If yes, complete and submit "Declaration of end of study" form, available on the HRA website	Yes
If no, what is the expected completion date? If you expect the study to overrun the planned completion date, what are the reasons for this?	
If you do not expect the study to be completed, give reason(s)	

4. Registration

Is the study a 'clinical trial'? (Defined as the first 4 categories on the IRAS filter page) (For CTIMPs, please use CTIMP progress reporting template)	Yes
Is the study registered on a publicly accessible database? (Registration of clinical trials is a condition of approval for studies approved after 30 September 2013)	Yes
If yes, please provide the name of the publicly accessible database and the registration number	Registration number: NCT04424745
If no:	a) What is the reason for non-registration? b) What are your intentions for registration?

5. Recruitment of participants

In this section, “participants” includes those who will not be approached but whose samples/data will be studied.

Number of participants recruited:	Proposed in original application: 100 Actual number recruited to date: 85
Number of participants completing the study:	Actual number completed to date: 80
Number of withdrawals from study to date due to: Total study withdrawals: 5	a) withdrawal of consent: 1 b) loss to follow-up: 4 c) death (where not the primary outcome)
*Number of treatment failures to date (prior to reaching primary outcome) due to: Total treatment failures: 0 *Applies to studies involving clinical treatment only	a) adverse events: 0 b) lack of efficacy: 0
Have there been any serious difficulties in recruiting participants?	No
If Yes, give details:	
Do you plan to increase the planned recruitment of participants into the study? Please note, any increase in planned recruitment or changes to the recruitment methodology should be notified to the REC as a substantial amendment for ethical review.	No

6. Safety of participants

Have there been any related and unexpected serious adverse events (SAEs) in this study?	No
Have these SAEs been notified to the Committee?	Not applicable

If no, please submit details with this report and give reasons for late notification.	
Have any concerns arisen about the safety of participants in this study? If yes, give details and say how the concerns have been addressed. This information may be considered by the Committee when reviewing the report.	No

7. Amendments

Have any substantial amendments been made to the study during the year?	Yes
If yes, please give the date and amendment number for each substantial amendment made.	SA01, 24.09.20

8. Serious Breaches of the Protocol

Have any serious breaches of the protocol occurred during the year? If Yes, please enclose a report of any serious breaches not already notified to the REC.	No

9. Other issues

Are there any other developments in the study that you wish to report to the Committee?	No

10. Declaration

*Signature/Electronic Signature of Chief Investigator or Sponsor representative:	
Print name:	Ulrike Schmidt
Date of submission:	23.02.22

Appendix C.8. End of study declaration

NHS
Health Research Authority

Declaration of the end of a study

(For all studies except Clinical Trials of Investigational Medicinal Products)

To be completed in typescript by the Chief Investigator or sponsor representative and submitted to the Research Ethics Committee (REC) that gave a favourable opinion of the research within 90 days of the conclusion of the study or within 15 days of early termination

For questions with Yes/No options please indicate answer in bold type.

1. Details of Chief Investigator

Name:	Professor Ulrike Schmidt
Address:	Dept. of Psychological Medicine, Section of Eating Disorders, IoPPN, PO-59, De Crespigny Park, London, SE5 8A5
Telephone:	020 7848 0181
E-mail:	Ulrike.schmidt@kcl.ac.uk

2. Details of study

Full title of study:	A feasibility study of neuromodulation with attention bias modification training for binge eating disorder
IRAS ID:	284609
Name of REC:	London - Fulham Research Ethics Committee
REC reference number:	20/LO/0936
Date of favourable ethical opinion:	06/08/2020

Sponsor	King's College London, South London and Maudsley NHS Foundation Trust

3. Study duration

Date study commenced:	01/02/2021
Date study ended	31/01/2022
Did this study terminate prematurely?	Yes

4. Recruitment

Number of participants recruited	100
Proposed number of participants to be recruited at the start of the study	85
If different, please state the reason or this	The trial was a feasibility trial and, as such, one aim was to assess recruitment and retention rates over the 12-month pilot period.

5. Circumstances of early termination

What is the justification for this early termination?	The trial was a feasibility trial and, as such, one aim was to assess recruitment and retention rates over the 12-month pilot period. Sample size recruited is similar to comparable feasibility trials so was considered acceptable.

6. Potential implications for research participants

Are there any potential implications for research participants as a result of terminating the study prematurely? Please describe the steps taken to address them.	None

7. Final report on the research

Is a summary of the final report on the research enclosed with this form?	No

8. Declaration

*Signature or Electronic Authorisation of Chief Investigator/sponsor representative: *Please print below or insert electronic signature	
Print name:	Ulrike Schmidt
Date of submission:	23.03.2022

Appendix C.9. FAST-R Service User Feedback Letter

NIHR | Maudsley Biomedical Research Centre

FAST-R Service Feedback

Date: 25/5/20

Study Title: A feasibility study of neuromodulation with attention bias modification training for binge eating disorder (TANDEM)

Submitted by: Michaela Flynn

Overall the four reviewers were positive towards this project and thought they it was a worthwhile topic area.

General comments are given here, and additional specific feedback is annotated on the attached word documents as track changes or comments.

Participant 1

Tandem Poster

- I understand the thinking behind including a tandem bike on the poster for a study whose acronym is TANDEM; however, my immediate thought was, is this an exercise-based intervention, which it isn't… The image is also very front and centre, which as someone with binge-eating disorder immediately set off feelings of guilt of oh I should be exercising more.

Tandem Roadmap

- Useful to have alongside the PIS but again, similar comments regarding the use of a tandem bike image.
- I would change this from a treatment roadmap to a full study roadmap including the screening, pre-treatment assessment, fasting, additional computer tasks, food diary, post-treatment assessment, final follow-up etc. as steps including the time taken for each as reading through the PIS, the study suddenly becomes quite overwhelming / you don't realise the extent / length of the study initially.

Participant 2

Tandem Poster
The TDCS with Attention Training TANDEM poster is good but not suitable to send out for computer reading as the text is too small. However, the content is good.

Tandem Roadmap
The TANDEM Treatment Road Map is very useful and easier to read on the computer.

Other
The Participants Information Sheet is too long and the title should be easier to read. Some

SUs with literacy problems will find this information difficult to read.

The pre-treatment and post treatment assessments seem long. 3 hours is a long time for an assessment online. Might put some SUs off the research study.

Adult consent form is good and very detailed but easy to read.

It is good that you are paying SUs for their time.

Participant 3

Other
Without wishing to sound negative because I have had a daughter with binge eating disorder so I know what a dreadful illness this is but that said I did not really feel happy with this whole piece of research from I suppose a safety angle. As I am not a professional or a researcher I am prepared to be challenged that my view should not be a worry. However the other questions I would ask are:

How many people are they hoping to recruit?
What happens if things go wrong in the home testing?
How do you know if the participants have followed it properly when on their own?

I am not sold on the title TANDEM nor on the poster as I think it tries to be too clever. Under "What are we doing?" I think the word tDCS should be spelt out. I feel a little bit the same about the route map.

Participant 4

Tandem Poster
Again, like the poster itself very much since it grabs your attention, but do need to put on poster that have to be generally healthy with normal vision, have no metal in body, no epilepsy and not be pregnant!

Tandem Roadmap
Like very much the roadmap – visual explanation gets interest and makes it more enjoyable

Other
All in all, a very well thought out bit of research, well written up and the PIS very easy and informative to read, even though apparently much longer than is usually thought to be ok.

Very happy with the consent form.

All other comments can be found in the documents attached.

Many thanks for using FAST R Service. We hope you have found it useful and please do let us know if you need any more support or feedback.

The NIHR Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust & King's College London

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Appendix C.10. Summary of Service user feedback

Summary of TANDEM Service User Feedback

IRAS Project ID: 284609

7 service user volunteers reviewed the TANDEM participant facing materials between the 14th and the 21st of May 2020 and responded to the questions below. Revisions were made to participant facing materials in response to their feedback. Here, a summary of their comments and feedback is presented with a selection of direct quotes. All quotes are anonymous.

1. The participant information sheet explained what attention training is, what tDCS is, and why we believe that combining these two treatments may be effective. Did you feel that this explanation was easy for you to understand? If not, are there specific areas or topics you feel we should revise?

   Overall, participants felt that the information was outlined comprehensively and clearly, and that the images of the tDCS equipment and treatment procedure was helpful for their understanding. Several participants suggested that an infographic representation of the study procedures, like the "Tandem treatment roadmap" which summarises the treatment procedure, would be very helpful for making the study procedures digestible.

   One participant highlighted examples of technical language and jargon on the first page of the PIS which they felt was " daunting, and made me feel unsure about my understanding of what you were doing". Another expressed that they would have liked more information about how they would be supported "to do this all at home by themselves", indicating to the research team that it was not sufficiently clear that all participants would be comprehensively trained in treatment procedures and remotely supervised by the research team. Finally, one participant said that while they understood that the risk for seizure was very rare, "it would be helpful to compare this risk to something we already do in everyday life". This has led to the addition of a sentence comparing the risk for seizure following tDCS administration to the risk for seizure associated with antidepressant medication.

2. You have previously taken part in a study that has used either attention training or tDCS, perhaps you have even had experience with both of these interventions. Do you feel that continued research looking at these interventions is worthwhile?

   All participants who provided feedback on study materials felt that this study was worthwhile. Some queried whether COVID-19 had prompted the investigation of self-administration at home, but felt that it was exciting to see COVID-19 "opening up new doors for them as patients".

3. The TANDEM study will be conducted entirely remotely. How do you feel about taking part in research like this from home? Do you have concerns about our expectation that participants attend appointments virtually (i.e., via a laptop based video call)? How do you feel about data being collected entirely online? Do you have concerns about the data security that we have not clearly addressed in the participant information sheet?

   Respondents generally felt comfortable about taking part at home. Three expressed some confusion about the amount the support participants would receive from the research team when taking part and felt that clearly outlining this in the information sheet would help to put those concerns at ease. No respondent expressed concerns about completing questionnaires or tasks online. One highlighted that the affiliation with reputable institutions gave them confidence in our attention to their confidentiality and data management.

4. Participants will be asked to complete many virtual appointments when taking part in

TANDEM. Specifically, there will be a training session focusing on teaching the participant to deliver tDCS at home, 3 assessments lasting 3 hours each, and 15 treatment sessions completed every weekday for 20 minutes over 3 – 4 weeks. In total, taking part will take about 15 hours. If you were taking part, would you feel that this number of training sessions, assessment sessions, and treatment sessions is acceptable?

Overall, participants felt that this was acceptable and held the view that more comprehensive assessments allowed for the research team to better assess whether the treatment works as intended. Some felt that completing 3 hour assessments online is very long, and that most people will need breaks during this time. The research team clarified that this time estimate include numerous breaks and agreed that it would be important to clarify this in the information sheet, and revise the estimated participation time to 2-3 hours, depending on the length and number of breaks taken. In addition, feedback has led to the revision of the final assessment time point, which now involves a substantially shorter assessment.

5. Above, we asked about how you felt about the amount of time we are asking participants to invest in this study. We are yet to decide on an appropriate amount for study payment and would be interested to know what amount of payment you feel would be valued by participants choosing to take part in this study.

   Views ranged widely on appropriate study payment, with some indicating they would be glad to be paid at all, and others suggesting £10-15 per hour would be suitable. In light of this feedback, the study budget, and participant views on the value of the treatment, we have decided that £50 compensation is appropriate. This payment can be viewed as £10 per hour for assessments, with no formal payment for treatment sessions.

6. In the TANDEM study, participants will self-administer tDCS (alongside attention training) at home. All participants will be supervised and supported by the researcher (via videocall). How do you feel about this? Do you feel that there are any factors that the research team may not have considered? Do you feel that there are any benefits to being able to deliver treatment at home?

   Participants felt comfortable with the procedure for supervising tDCS and many expressed that they saw benefits to being able to take part at home, including time saved on travel, convenience (particularly when considering child care), and the opportunity to take part if living outside of London.

7. What did you think about our poster? Was there information missing that you think should be there? Was the information easy to read and understand? Was it eye catching? Did you feel that the “branding” was inviting and exciting?

   Respondents felt very positive about the study advertisements and expressed strong feedback about the professional look and feel of the poster. Some felt that the tandem bike could confuse people about the study focus, leading people to believe that we are looking at exercise rather than a treatment, but most listed the bike as a highlight. In response to this we have prepared additional advertisements that may stand out to different audiences and ensure comprehension.

8. How did you feel about the infographic summarising the treatment process (the TANDEM Roadmap)? Was this easy to understand and useful for getting your head around what the treatment might be like?

   Views on the Tandem Roadmap were overwhelmingly positive and that it “demystified the process” and “made it all seem very exciting and friendly”. Numerous respondents felt that a similar visual should be prepared to summarise the study overall.

Appendix D. Participant information sheets

Appendix D.1. TANDEM participant information sheet

PARTICIPANT INFORMATION SHEET

Combining attention training with neuromodulation for binge eating disorder (TANDEM)

IRAS Project ID: 284609
Research Ethics Committee reference number: 20/LO/0936

This feasibility study will look at the whether combining two novel treatments may improve symptoms of binge eating disorder. Both interventions have been shown to improve eating disorder symptoms when used separately. We'll be looking at whether these benefits are enhanced when the treatments are combined. Before you decide whether you want to take part, it is important that you understand why the research is being done and what taking part will involve. Please read this information sheet carefully and discuss any questions you have with the research team.

Part One: Key Information

What is the purpose of the study?
Binge eating disorder is a common mental health problem which is often related to obesity, distress, and poor quality of life. At present, many people do not fully recover with treatment and some face challenges accessing treatment. For this reason, exploring new, accessible options for treatment is important.

Both attention training and transcranial direct current stimulation (tDCS) have been shown improve symptoms in people with binge eating disorder. Attention training aims to change automatic responses to food which are driven by the frontal areas of the brain. TDCS is a non-invasive brain stimulation technique used to increase or decrease activity in specific regions of the brain. It may be used to change the activity in these frontal regions known to be involved in binge eating behaviour. Recent studies using tDCS in people with binge eating disorder have shown that tDCS may reduce food intake, cravings for food and the urge to binge. Importantly, tDCS is a safe and well tolerated procedure which, with the appropriate training, supervision, and support, can safely be delivered at home.

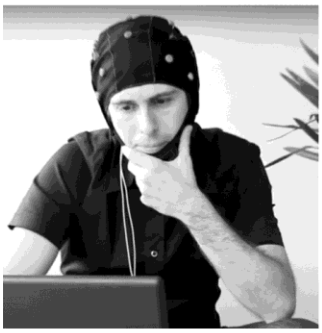
We think that both attention training and tDCS may produce the benefits we see by causing changes to similar parts of the brain. As such, delivering both treatments together may have a stronger effect on eating disorder symptoms than either of the treatments alone. The TANDEM study will look at the effects of combining attention training with self-administered tDCS in people with binge eating disorder. This will be the first study to look at the effects of this specific combination of interventions in people with binge eating disorder and will be the first study to train and support participants with binge eating disorder to delivered tDCS at home.

Why have I been invited?
You are invited to participate if you are aged 18 to 60 years, you currently meet criteria for binge eating disorder, and you are overweight or obese. As handedness (i.e., being right or left handed) has been shown to influence our brain organisation, all participants will need to be right handed. Participants will also need access to a laptop or desktop computer with webcam.

You will not be able to take part if you have a visual impairment that cannot be corrected by glasses or contact lenses. For safety reasons, you will be asked to tell us if you have any metal anywhere in your body, if you have a history of epilepsy, seizure or brain injury and if you have any other significant physical or mental health conditions. If we believe that it may be unsafe for you to self-administer tDCS, you will not be able to take part. Similarly, for safety reasons participants are not eligible to take part if they are pregnant. All biologically female participants will be asked whether they are (or may be) pregnant.

Do I have to take part?
You do not have to take part in this study. If you do take part, you will be free to withdraw at any time, without giving a reason. After you have spoken with a researcher and your eligibility has been confirmed, you will have 2 weeks to decide whether you would like to participate. Your normal clinical care will not be affected if you chose not to take part.

What treatment will I receive?



Attention Training
Attention training is a computer-based activity which targets automatic processes driving attention. During training you will be asked to look towards or away from images of food, depending on the instruction given by the task.

Transcranial direct current stimulation
TDCS is a comfortable and non-invasive procedure. During tDCS, a continuous electric current of low intensity passes between 2 electrodes placed over the scalp. This electrical stimulation increases brain activity in brain areas below. Stimulation takes 20 minutes. The picture above on the left shows a person receiving tDCS while completing a computer task, just as you would be doing if you took part. They wear a cap on their head which places the electrodes in the right place on the scalp. The stimulation is started and stopped using the device pictured on the right. Before beginning treatment, you will be trained to you to use this equipment safely. The researcher will also supervise you via videocall during your treatment sessions, to make sure that you feel comfortable and safe at all times.

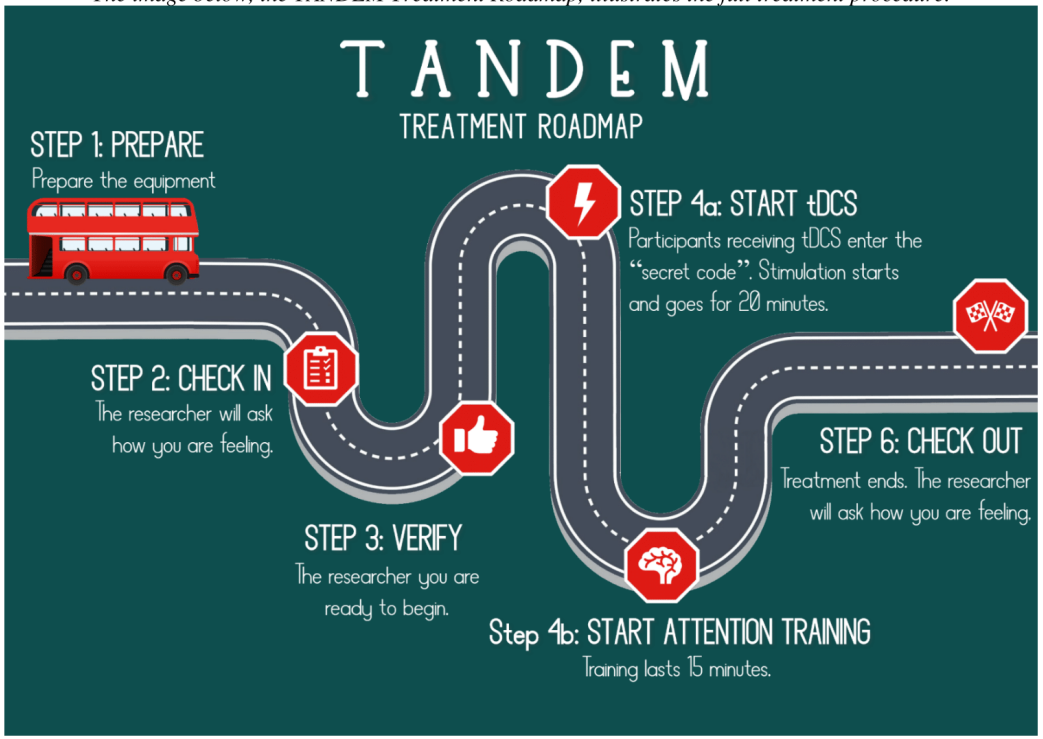
All participants in the TANDEM study receive treatment however, not everyone will receive the same treatment. Participants will be randomly allocated to one of four different treatment groups. These are a) real tDCS with attention training, b) sham (placebo) tDCS with attention training, c) attention training only, or d) a waitlist for attention training. Those allocated to the waitlist complete all research activities over a 2-week period before they begin attention training. Their role in the study is to be a comparison group which will allow us to assess whether changes following treatment may be explained by the treatment itself, or whether they may simply occur by chance.

If you receive tDCS, you will not know whether the stimulation you receive is real or sham; sham tDCS looks and feels just like real tDCS. If you are not happy that you may receive sham stimulation or no stim during this study, you should not take part.

Treatment Procedure
Treatment sessions are completed every weekday for 2-3 weeks, until a total of 10 sessions have been completed. Each session lasts 20 minutes. You will be instructed to find a comfortable seated position in front of a laptop or desktop computer and set up the tDCS equipment as you were taught during your training. When you are ready, the researcher will check in with you to find out

how you are feeling, then they will give you a special code which you use to start the stimulation. This code can only be used once and changes every day. When the stimulation begins you may feel a tingling sensation on you scalp. After a minute has passed, you will start the attention training on the computer in front of you. This training takes 15 minutes. When you have finished, you will stay seated until the stimulation ends. After each session, the researcher will ask you about any discomfort you experienced and ask about how you are feeling.

The image below, the TANDEM Treatment Roadmap, illustrates the full treatment procedure.



What will happen to me if I take part and what will I have to do?
After reading this information sheet you will need to complete a consent form and provide contact information for your GP and, where relevant, your eating disorder therapist.

Screening
You will then have a 20-minute screening call with a researcher. During this call the researcher will ask you questions about your eating, your medical and psychiatric history, and your general mental health. If, after completing this call you are eligible, you will be invited to take part. You may take up to 2-weeks to decide whether you would like to participate. If you decide to take part, you will be randomly allocated to one of the four groups (attention training with real tDCS, attention training with sham tDCS, attention training only, or 6-week wait list followed by attention training).

tDCS Training (tDCS groups only)
You will be loaned all the equipment needed for you to deliver tDCS at home. Before beginning treatment, you will complete a 45 minute tDCS training session with the researcher. This session is completed via videocall. During the training you will learn about how tDCS works, the risks associated with tDCS and how to manage these, and the procedure for safely administering tDCS. If you or the researcher feel that you need more training and practice using the tDCS equipment, further training will be provided.

Baseline Assessment
Three days before you begin treatment or your time on the wait list, you will complete an online pre-treatment assessment which will take 2.5 - 3 hours inclusive of regular breaks. You will be asked to fast for 3 hours before this assessment. This helps to ensure that the amount of time since eating last is similar for all participants. You will complete the pre-treatment assessment at home on a laptop or desktop computer with a webcam. The researcher will join you via video call to provide instructions and to answer any questions that you have along the way. This call will continue for the full assessment however, you will be invited to turn off your camera and microphone when completing tasks. That way you can concentrate effectively and feel more comfortable answering questions freely.

During the assessment you will complete questionnaires about your eating behaviour, your mood, and your day to day life. You will also complete computer tasks looking at attention, memory, and decision making. These questionnaires and tasks can be tiring, so you will be encouraged to take regular breaks throughout. At the end of this session, you will be given a link to an online food diary where you will log everything that you eat or drink (aside from water) over the following 48 hours.

Treatment
Your treatment will vary depending on the group you have randomly been assigned to.

If you are receiving attention training with real or sham tDCS:
During this study you will complete 10 sessions of combined attention training with tDCS over 2-3 weeks. A typical course of treatment involves 5 consecutive sessions completed each weekday (i.e., Monday to Friday), at approximately the same time each day, with no treatment completed on the following two days (Saturday and Sunday). This will continue until a total of 10 sessions have been completed. For the first 5 sessions, you will be closely supervised by the researcher via video call. Thereafter, supervision will be offered as needed or requested.

Each session of combined attention training and tDCS will last 20 minutes. You will be instructed to find a comfortable seated position in front of the laptop or desktop computer and set up the tDCS equipment as you were taught during your training. The researcher will support and supervise you as you do this until you feel confident setting up independently.

When you are ready, you will enter a special code into the tDCS machine and the stimulation will begin. When the stimulation starts you may feel a tingling sensation on you scalp. After a minute

has passed, you will begin the attention training on the computer in front of you. This training takes approximately 15 minutes. When you have finished, you will stay seated until the stimulation ends.

After each treatment session, the researcher will ask you about any discomfort you experienced and ask you to answer some short questions about how you are feeling.

If you are receiving attention training only:
You will complete 10 sessions of attention training over 2-3 weeks. A typical course of treatment involves 5 consecutive sessions completed each weekday (i.e., Monday to Friday), at approximately the same time each day, with no treatment completed on the following two days (Saturday and Sunday). This will continue until a total of 10 sessions have been completed. You will be supervised by the researcher via video call.

Each session of will last 20 minutes. You will be instructed to find a comfortable seated position in front of the laptop or desktop then, when you are ready, you will begin the attention training on the computer in front of you. This training takes approximately 15 min.

If you are allocated to the waitlist:
You will not receive any treatment for 2-weeks. Following this you will receive attention training as described above.

2-week and 6-Week Follow Up
After 2 weeks have passed (i.e., those receiving treatment have finished all sessions, and those on the wait list have waited for two weeks) you will be asked to complete the second assessment. This assessment is very similar to the one completed at baseline. 6-weeks after this you will complete a final assessment. This assessment is shorter than the previous two, lasting about 1 hour. It involves completing a selection of questionnaire measures and tasks from previous assessments. You will be asked to fast for 3 hours before each assessment.

Once all assessments have been completed participants on the waitlist will be invited to start attention training. Similarly, for those who received tDCS the researcher will be able to tell you whether the stimulation you received was real or sham. As all participants will have received real attention training, which has been demonstrated to improve symptoms of binge eating disorder, we will not be offering participants who received sham tDCS the opportunity to repeat the treatment with real tDCS. This is because, at this stage, we do not know that combining attention training with tDCS is associated with superior effects from treatment.

Optional Interview
In addition to the tasks described above, you will also be invited to take part in an optional interview about your experience taking part in this study. You do not have to take part in this interview; it is optional.

The full participation journey is illustrated on the next page.

Compensation and Study Payment
All participants will be paid a total of £50 for taking part. This payment will be made over 2 instalments: £30 will be paid to you after you have completed the 2-week follow up and, where relevant, you have returned the tDCS equipment to the research team. Then, £20 will be paid to you after completing the 6-week follow up assessment.

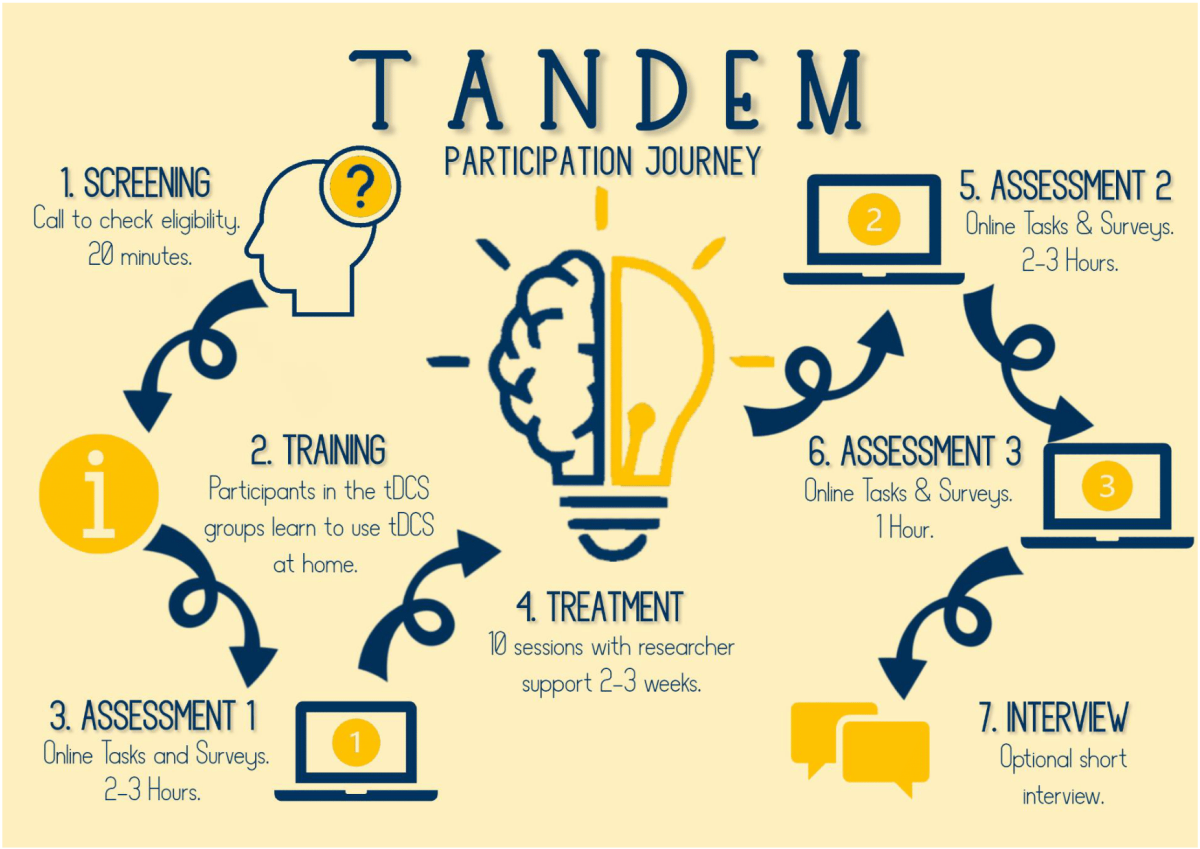
What are the possible benefits of taking part?
All participants will receive real attention training. Attention training has been shown to improve symptoms of binge eating disorder so you may experience some benefits in relation to your eating behaviour. There is also some evidence to suggest that stand-alone tDCS is associated with improved eating disorder symptoms, so it is possible that those who receive real tDCS may experience a more pronounced change in their eating disorder symptoms.

What are the possible disadvantages and risks of taking part? What are the side effects?
Some people may find some of the study procedures tiring and slightly uncomfortable. If you do experience discomfort or side effects, you are free to stop at any time without giving a reason.

There are no significant risks associated with the training. TDCS is safe and well tolerated. Common side effects include mild discomfort at the time of administration (i.e. tingling or itching sensation, and occasional redness on the scalp). The most serious side effect that has been reported is seizure, though this is very rare (< 0.01% of cases). By comparison, the risk for seizure following use of commonly prescribed antidepressant drugs is substantially higher, with seizures reported in 1-5% of cases depending on the drug. If you do experience any discomfort or side effects, you are free to stop taking part without giving a reason.

To ensure your safety, we will ask you lots of questions at screening about your medical history. These questions allow us to check whether you may be more at risk than others of experiencing adverse side effects. If we believe that you may be at risk, you will not be able to take part.

In this study, tDCS will be administered by the participant at home, with researcher supervision. Self-administration of tDCS by participants is common, simple, and safe. You will be given comprehensive tDCS prior to beginning treatment. If it you or the researcher feel that you are not confident administering tDCS home, for safety reasons, you will be withdrawn from the study.


TANDEM
PARTICIPATION JOURNEY
1. SCREENING
Call to check eligibility.
20 minutes.
2. TRAINING
Participants in the tDCS groups learn to use tDCS at home.
3. ASSESSMENT 1
Online Tasks and Surveys.
2-3 Hours.
4. TREATMENT
10 sessions with researcher support 2-3 weeks.
5. ASSESSMENT 2
Online Tasks & Surveys.
2-3 Hours.
6. ASSESSMENT 3
Online Tasks & Surveys.
1 Hour.
7. INTERVIEW
Optional short interview.

Part Two: Additional Information

What will happen to the results of the research study?
If you would like, the research team will send you a summary of the findings when the study is completed. The results from this project will also be included in postgraduate, masters and undergraduate reports, presented at conferences and educational events, and sent to a medical journal for publication. All reports and presentations will be written in such a way that no-one can work out who took part.

What if new information about the treatment becomes available during the study?
This is highly unlikely however, if it does, you will be informed immediately.

What will happen if I don't want to carry on with the study?
You can stop taking part at any time without giving a reason. If you decide to stop taking part, we will keep any data collected up to the time of your withdrawal.

Will participation affect my routine healthcare, or the waiting time for specialist treatment?
No. Participation in this study will have no impact on treatment as usual or wait time for care.

Participation in future studies?
If you take part in TANDEM you will be asked whether you wish to be notified about future research by our group. You do not have to agree to be contacted in the future. This is optional. If you do consent to be notified about future research, your name and contact information will be used by the TANDEM researcher ream to notify you about future studies you may be interested in.

What if there is a problem?
In the unlikely event that something does go wrong and you are harmed during the research you may have grounds for legal action for compensation against King's College London and/or South London and Maudsley (SLaM) NHS Foundation Trust, but you may have to pay your legal costs.

If you have a concern about any aspect of the study, please talk to the research team first. You can contact Michaela Flynn by email at michaela.flynn@kcl.ac.uk or by phone at 020 7848 0183. You may also contact SLaM Patient Advice and Liaison Service (PALS) by calling 0800 731 2864 or emailing pals@slam.nhs.uk.

If you remain unhappy and wish to make a formal complaint, please contact Dr Gill Dale, the Director of Research Quality and Head of the joint SLaM NHS Trust and IoPPN R&D Office (Email: gill.dale@kcl.ac.uk)

Will my participation be kept confidential?
All information which is collected during this study will be kept strictly confidential according to the General Data Protection Regulation (GDPR), brought into effect on 25th May 2018.

For your safety, we can only include you in the study if we notify your GP and, where relevant, your eating disorders therapist. Therefore, it is necessary that they know about your involvement in the trial. Similarly, if you experience distress while taking part, or if there are any concerns for yours or someone else's safety, we may be obliged to inform your GP, clinical care team, or relevant authorities. If we needed to do this, we would tell you first.

How will we use information about you?
We will need to use information collected from you for this research project. This information will include your name, contact information and date of birth. If you are taking part from outside of London, the tDCS equipment may need to be sent to your home address by courier. In this instance, your name and address will be shared with the courier company. Otherwise, only

members of the research team (Ms Michaela Flynn, Prof Iain Campbell, and Prof Ulrike Schmidt) will have access to your name, address and contact information. People who do not need to know who you are will not be able to see your name or contact details. Your data will only be used by the research team at King's College London. Your data will not be shared with any third party.

We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

This study will be conducted in the United Kingdom and is sponsored by King's College London and South London and Maudsley NHS Foundation Trust (SLaM). They will act as the data controller. The data protection officer is Albert Chan (email info-compliance@kcl.ac.uk).

Where can I find out more about how my information is used?
You can find out more about how we use your information at www.hra.nhs.uk/information-about-patients/ or by asking a member of the research team.

What are your choices about how your information is used?
We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Insurance/indemnity
In the event that something does go wrong and you are harmed during the research you may have grounds for legal action for compensation against King's College London, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate). King's College London has obtained insurance which provides no-fault compensation i.e. for non-negligent harm, you may be entitled to make a claim for this.

Who is organising the research?
This study is being conducted as part the King's College London Doctor of Philosophy in Psychological Medicine programme (PhD programme) being completed by Michaela Flynn. This study is being funded by King's College London and the NIHR Maudsley BRC funding for investigations relating to Obesity, Lifestyle and Learning from Extreme Phenotypes. The study is co-sponsored by King's College London and South London and Maudsley NHS foundation Trust.

This research was reviewed by a team with experience of mental health problems and their carers who have been specially trained to advise on research proposals and documentation through the Feasibility and Acceptability Support Team for Researchers (FAST-R): A free, confidential service in England provided by the National Institute for Health Research Maudsley Biomedical Research Centre via King's College London and South London and Maudsley NHS Foundation Trust.

This study has been reviewed and given favourable opinion by the Fulham Research Ethics Committee.

Further information and contact details

Michaela Flynn (Email: michaela.flynn@kcl.ac.uk; Phone: 020 7848 0183)
Section of Eating Disorders, Department of Psychological Medicine
KCL Institute of Psychiatry, Psychology and Neuroscience,
16 De Crespigny Park
London, SE5 8AF

Appendix D.2. TANDEM participant information sheet for optional interviews about the treatment experience

PARTICIPANT INFORMATION SHEET

Brain Stimulation with attention training for binge eating disorder

Optional Interview about the Participant Experience

IRAS Project ID: 284609
Research Ethics Committee reference number: 20/LO/0936

We would like to invite you to participate in a study that is being conducted by a PhD student for research and educational purposes. 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. Please ask if there is anything that is not clear or if you would like more information.

What is the purpose of the study?
There is a need to develop new treatments who have difficulties with binge eating. In the TANDEM study we looked at whether simultaneous transcranial direct current stimulation (tDCS) and attention training affected eating behaviour and wellbeing. This was the first study to combine this specific form of attention training with tDCS in people with binge eating disorder. We would like to understand more about the individuals' experience of participation, their initial expectations of the intervention and their thoughts about the strengths and weaknesses of the treatment, and their ideas about ways to improve the intervention experience. We are also very interested to hear about your views on tDCS self administration.

Do I have to take part?
You do not have to take part in this interview; it is your choice. If you decide to take part, you will be asked to sign two identical consent forms. You will be free to withdraw from the study at any time without giving a reason. Your normal clinical care will not be affected if you chose not to take part.

What will happen to me if I take part and what will I have to do?
If you decide to take part, you would be invited to a virtual face-to-face interview. This interview should last approximately 45 minutes. This will be an individual session with just yourself and the researcher present. Before the interview takes place, we will give you this information sheet to keep and ask you to complete a consent forms. Once completed, a copy of the consent form will be sent to you to keep, and a copy will be kept by the research team for their records. The researcher will then discuss the interview procedure with you, and you will have the opportunity to ask any questions that you might have.

During the interview, we will ask you a series of questions which have been selected to capture a broad range of topics relating to your treatment experience. The interview will centre on your experiences (e.g., your initial expectations, hopes and concerns about the treatment intervention, any positive and negative aspects of completing the treatment/assessment sessions, and changes to yourself/your life that you have noticed since taking part in the study, etc.) You do not have to answer any questions that you do not want to. With your permission, we will audio record the interview to make sure that we don't miss any important points.

What are the risks of taking part in this study?
There are no major risks in taking part in this study. We do not anticipate that you will find the interview questions upsetting or uncomfortable; however, if this is the case, you may ask the interviewer to move on to the next topic or let them know that you would like to stop your participation.

What are the benefits of taking part in this study?
There are no direct benefits to taking part. We hope that you will find reflecting on your experience receiving the combined treatment helpful and enjoyable. The findings from this study are likely to provide important knowledge which will help us to develop better treatments for people with binge eating difficulties in the future.

Will I receive any payment?
Yes. You will receive £10 for your time and efforts.

Will participation in this study affect my routine healthcare, or the waiting period for specialist care?
No. Participation in this study will have no impact on your treatment-as-usual or waiting time for specialist care. We fully encourage you to begin treatment as provided by a health care professional as soon as it becomes available to you.

What will happen to the results of the research study?
If you would like, the research team will send you a summary of the findings when the study is completed. The results from this project will also be included in postgraduate, masters and undergraduate reports, presented at conferences and educational events, and sent to a medical journal for publication. All reports and presentations will be written in such a way that no-one can work out who took part.

What will happen if I don't want to carry on with the study?
You can stop taking part at any time without giving a reason. If you decide to stop taking part, we will keep any data collected up to the time of your withdrawal.

What if there is a problem?
In the event that something does go wrong and you are harmed during the research you may have grounds for legal action for compensation against King's College London and/or South London and Maudsley (SLaM) NHS Foundation Trust, but you may have to pay your legal costs.

If you have a concern about any aspect of the study, please talk to the research team first. You can contact Michaela Flynn by email at michaela.flynn@kcl.ac.uk or by phone at 020 7848 0183. You may also contact SLaM Patient Advice and Liaison Service (PALS) by calling 0800 731 2864 or emailing pals@slam.nhs.uk.

If you remain unhappy and wish to make a formal complaint, please contact Dr Gill Dale, the Director of Research Quality and Head of the joint SLaM NHS Trust and IoPPN R&D Office (Email: gill.dale@kcl.ac.uk)

Will my participation be kept confidential?
All information which is collected during this study will be kept strictly confidential according to the General Data Protection Regulation (GDPR), brought into effect on 25th May 2018. Your personal information and audio data will remain confidential at all times. It will also remain anonymous to everyone apart from the primary researchers (Michaela Flynn, Prof Ulrike Schmidt and Prof Iain Campbell). However, if you tell us something that makes us believe that you or someone else is unsafe, we may be obliged to disclose this to healthcare professionals or relevant authorities. If we needed to do this, we would tell you first.

How will we use information about you?
We will need to use information collected from you for this research project. This information will include your name, contact information and date of birth. Only members of the research team (Ms Michaela Flynn, Prof Iain Campbell and Prof Ulrike Schmidt) will have access to your name and contact information. People who do not need to know who you are will not be able to see your name or contact details. Your data will only be used by the research team at King's College London. Your data will not be shared with any third party.

We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

This study will be conducted in the United Kingdom and is sponsored by King's College London and South London and Maudsley NHS Foundation Trust (SLaM). They will act as the data controller. The data protection officer is Albert Chan (email info-compliance@kcl.ac.uk).

What are your choices about how your information is used?
We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Participation in future studies?
If you take part in TANDEM you will be asked whether you wish to be notified about future research by our group. You do not have to agree to be contacted in the future. This is optional. If you do consent to be notified about future research, your name and contact information will be used by the TANDEM researcher ream to notify you about future studies you may be interested in.

Where can I find out more about how my information is used?
You can find out more about how we use your information at www.hra.nhs.uk/information-about-patients/ or by asking a member of the research team.

Insurance/indemnity
In the event that something does go wrong and you are harmed during the research you may have grounds for legal action for compensation against King's College London, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate). King's College London has obtained insurance which provides no-fault compensation i.e. for non-negligent harm, you may be entitled to make a claim for this.

Who is organising the research?
This study is being conducted as part the King's College London Doctor of Philosophy in Psychological Medicine programme (PhD programme) being completed by Michaela Flynn. This study is being funded by King's College London and the NIHR Maudsley BRC funding for investigations relating to Obesity, Lifestyle and Learning from Extreme Phenotypes. The study is co-sponsored by King's College London and South London and Maudsley NHS Foundation Trust.

This research was reviewed by a team with experience of mental health problems and their carers who have been specially trained to advise on research proposals and documentation through the Feasibility and Acceptability Support Team for Researchers (FAST-R): A free, confidential service in England provided by the National Institute for Health Research Maudsley Biomedical Research Centre via King's College London and South London and Maudsley NHS Foundation Trust.

This study has been reviewed and given favourable opinion by the London and Fulham Research Ethics Committee.

Further information and contact details
If you have any questions or want more information, please contact Michaela Flynn

Email: michaela.flynn@kcl.ac.uk
Phone: 020 7848 0183)
Section of Eating Disorders, Department of Psychological Medicine
KCL Institute of Psychiatry, Psychology and Neuroscience,
16 De Crespigny Park
London, SE5 8AF

Appendix D.3. Participant information sheet for the study of Cognitive Control Functions in Binge Eating Disorder and Obesity (CoCo)

PARTICIPANT INFORMATION SHEET

Cognitive Control in Binge Eating Disorder and Obesity (CoCo)

Research Ethics Committee Reference Number: LRS-20/21-20873

This study will look at brain functioning in adults with obesity. We are particularly interested in understanding whether brain functioning is different for obese adults with binge eating disorder, relative to those without binge eating disorder. Before you decide whether you want to take part, it is important that you understand why the research is being done and what taking part will involve. Please read this information sheet carefully and ask any questions you may have.

What is the purpose of the study?
Binge eating disorder is a common mental health problem which is often related to obesity. However, few studies have looked at if and how obese adults with and without BED differ in terms of the way they think. For this reason, CoCo will collect data on brain functioning from adults with obesity and binge eating disorder, and adults with obesity only. Using this data, we will look at whether there are differences between the groups, and whether there are factors that may explain these differences. In doing so, we hope to gain valuable insights which may contribute to improvements for treatment for both binge eating disorder and obesity.

Why have I been invited?
You are invited to participate if you are aged 18 to 60 years and meet the current World Health Organisation criteria for obesity. Please note that in order to take part you will need access to a laptop or desktop computer with webcam.

You will not be able to take part if you have a visual impairment that cannot be corrected by glasses or contact lenses or if you have any other significant physical or mental health conditions that may be related to brain functioning.

What will happen to me if I take part and what will I have to do?
After reading this information sheet you will need to complete an online consent form.

You will then have a 15-minute screening call with a researcher. During this call the researcher will ask you questions about your eating, your medical and psychiatric history, and your general mental health. If, after completing this call you are eligible, you will be invited to take part. You may take up to 2-weeks to decide whether you would like to participate.

If you decide to take part, you will be booked in to complete a 2-hour online assessment. This assessment is completed in your home on a laptop or desktop computer with a webcam. The researcher will join you via video call to provide instructions and to answer any questions that you have along the way. This call will continue for the full assessment however, you will be invited to turn off your camera and microphone when completing tasks. That way you can concentrate effectively and feel more comfortable answering questions freely.

You will be asked to fast for 3 hours before this assessment. This helps to ensure that the amount of time since eating last is similar for all participants.

During the assessment you will complete questionnaires about your eating behaviour, your mood, and your day to day life. You will also complete computer tasks looking at attention, memory, and decision making. These questionnaires and tasks can be tiring, so you will be encouraged to take regular breaks throughout to minimise fatigue.

Do I have to take part?
You do not have to take part in this study. Participation is completely voluntary. You should only take part if you want to and choosing not to take part will not disadvantage you in anyway. If you decide to take part we will ask you to sign a consent form and you will be given a copy of this consent form to keep. You will then be invited for screening and, if eligibility is confirmed, you will have 2 to decide whether you would like to participate. Importantly, if you will be free to withdraw at any time, without giving a reason.

Compensation and Study Payment
As a token of thanks for the time and effort you invest in take part you will receive £15.

What are the possible benefits of taking part?
There are no direct benefits to taking part in this study, though may participants find the experience of taking part in research rewarding.

What are the possible disadvantages and risks of taking part?
You will be asked questions about your eating and your mental wellbeing. Sometimes these questions can be distressing, or you may feel uncomfortable about answering them. If this happens, know that you can withdraw at any time without giving a reason. Also, the research team will be there to support you, and will assist you to access support if you need it.

You may also find that you experience tiredness or fatigue when completing length questionnaires or computer-based tasks. To make sure you feel comfortable throughout, you will be encouraged to take regular breaks. There are no other anticipated disadvantages or risks associated with taking part.

What will happen to the results of the research study?
If you would like, the research team will send you a summary of the findings when the study is completed. The results from this project will also be included in postgraduate, masters and undergraduate reports, presented at conferences and educational events, and sent to a medical journal for publication. All reports and presentations will be written in such a way that no-one can work out who took part.

What will happen if I don't want to carry on with the study?
You can stop taking part at any time without giving a reason. If you wish to withdraw your data, you will need to notify us of this by the 31st of December 2021. Following this, data will be anonymised and withdrawal will no longer be possible.

Participation in future studies?
If you take part in CoCo you will be asked whether you wish to be notified about future related research by our group. You do not have to agree to be contacted in the future. This is optional. If you do consent to be notified about future research, your name and contact information will be retained by the researcher ream to notify you about future studies you may be interested in.

Will my participation be kept confidential?

All information which is collected during this study will be kept strictly confidential according to the General Data Protection Regulation (GDPR), brought into effect on 25th May 2018. If you would like more information about how your data will be processed in accordance with GDPR please visit the link below:

https://www.kcl.ac.uk/research/support/research-ethics/kings-college-london-statement-on-use-of-personal-data-in-research

How will we use information about you?
We will need to use information collected from you for this research project. This information will include your name, contact information and date of birth. Only members of the research team (Ms Michaela Flynn, Prof Iain Campbell, and Prof Ulrike Schmidt) will have access to your identifiable information. People who do not need to know who you are will not be able to see your name or contact details. Your data will only be used by the research team at King's College London. Your data will not be shared with any third party.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

We will keep all information about you safe and secure and we will write our reports in a way that no-one can work out that you took part in the study. Once we have finished the study, your data will be anonymised and retained for 10 years. This means that your anonymised data may be included in future related studies.

What if something goes wrong?
If during this study you are harmed 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:

Professor Ulrike Schmidt: ulrike.schmidt@kcl.ac.uk

Who is organising the research?
This study is being conducted as part the King's College London Doctor of Philosophy in Psychological Medicine programme (PhD programme) being completed by Michaela Flynn. This study is being funded by King's College London and the NIHR Maudsley BRC funding for investigations relating to Obesity, Lifestyle and Learning from Extreme Phenotypes. The study is co-sponsored by King's College London and South London and Maudsley NHS foundation Trust.

This research was reviewed by a team with experience of mental health problems and their carers who have been specially trained to advise on research proposals and documentation through the Feasibility and Acceptability Support Team for Researchers (FAST-R): A free, confidential service in England provided by the National Institute for Health Research Maudsley Biomedical Research Centre via King's College London and South London and Maudsley NHS Foundation Trust.

This study has been reviewed and given favourable opinion by the King's College London Research Ethics Committee (reference: LRS-20/21-20873)

Further information and contact details

Michaela Flynn (Email: michaela.flynn@kcl.ac.uk; Phone: 020 7848 0183)
Section of Eating Disorders, Department of Psychological Medicine
KCL Institute of Psychiatry, Psychology and Neuroscience,
16 De Crespigny Park
London, SE5 8AF

Appendix E. Consent forms

Appendix E.1. TANDEM Study Consent Form

ADULT CONSENT FORM FOR PARTICIPANTS IN THE TANDEM STUDY

Please complete this form after you have read the participant information sheet and listened to an explanation about the research.

Research Ethics Committee Reference: 20/LO/0963 *IRAS ID: 284609*

Thank you for thinking about taking part in this research. The person organising the research must clearly explain the research to you and allow you to ask any questions you may have. If you have any questions, please discuss them with the researcher before deciding to participate. You will be given a copy of this consent form to keep and refer to at any time.

Please indicate your consent by typing your initials in the box below each point.

- I have read and understood the participant information sheet (V4, 30/07/2020). I have had the opportunity to consider the information and ask questions.

- I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason, and without my medical care or legal rights being affected.

- 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 General Data Protection Regulation (GDPR, 2018). 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.

- I understand that my GP, and where relevant eating disorders therapist, will be informed about my participation in this study.

- I understand that the relevant sections of my medical notes and data collected during the study may be looked at by individuals from King's College London, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

- I understand that I will be trained to self-administer transcranial direct current stimulation (tDCS) that my ability to do so safely will be assessed by the researcher. I understand that I may not be able to take part if I cannot safely self-administer tDCS.

- I agree to take part in the above study.

- **OPTIONAL**: I would like the researcher team to send me a summary of the study findings.

- **OPTIONAL:** I consent to being contacted by King's College London researchers about follow up studies or future studies of a similar nature.

Participant's Statement:

I agree that the TANDEM research project has been explained to me to my satisfaction and I agree to take part in the study. I have read the information included in this form and the participant information sheet and I understand what the study involves.

Signed:

Date:

Time:

Investigator's Statement:

I confirm that I have explained the nature, demands and any foreseeable risks of the proposed research to the participant.

Signed:

Date:

Time:

Witness Statement:

I confirm that procedures for informed consent have been followed in line with study protocol.

Signed:

Date:

Time:

Enquiries:

Michaela Flynn
Eating Disorders Research Group
Institute of Psychiatry, Psychology & Neuroscience,
De Crespigny Park,
London, SE5 8AF

Phone: 020 7848 0183 Email: michaela.flynn@kcl.ac.uk

Appendix E.2. TANDEM letter to general practitioners/clinicians

GP/CLINICIAN LETTER: NOTICE OF PARTICIPATION IN RESEARCH

Title of Study: A feasibility study of neuromodulation with attention bias modification training for binge eating disorder (TANDEM)

REC reference number: 20/LO/0936 Date:

Dear

This letter is to inform you that your patient _____ (d.o.b: / /) has provided written consent to participate in a research study being undertaken at the Institute of Psychiatry, Psychology & Neuroscience at the Maudsley.

The project, overseen by Prof. Ulrike Schmidt and Prof. Iain Campbell, and will investigate the therapeutic effects of combining Attention Bias Modification Training (ABMT) with Transcranial Direct Current Stimulation (tDCS) in adults with binge eating disorder. Participation involves completing 15 sessions of concurrent ABMT with real or sham tDCS over 3-4 weeks.

ABMT is a computerised training that aims to alter responses towards food that people are not consciously aware of. During ABMT, participants are trained to 'look towards' low-calorie food and 'look away' from high-calorie food. Studies in binge eating disorder and obesity have shown that ABMT alone reduces attention biases towards food and improves ability to disengage with food stimuli.

TDCS is a safe, well tolerated, non-invasive form of brain stimulation which is suitable for supervised self-administration. In tDCS, a continuous electric current of low intensity is passed between 2 electrodes placed over the scalp, for 10 to 30 minutes, to stimulate the underlying brain tissue. It is proposed that by increasing neuroplasticity, TDCS may lead to lasting changes in brain function. Studies applying tDCS to the dorsolateral prefrontal cortex, a brain area believed to be critically involved in attentional control and self-regulation, have reported reduced craving for food and food consumption. In binge eating disorder, small studies have shown that tDCS may produce therapeutic effects, including reduced binge frequency, reduced craving for food and improved mood. During this study, your patient will be trained and supervised during self-administration of tDCS at home.

There are no known risks associated with ABMT. TDCS can cause mild discomfort at this stimulation site (tingling, burning, itching) however serious side-effects (e.g., seizure) are rare (<0.01%).

The information sheet attached to this letter provides further information about the study objectives and procedures. Please review this and contact us if you have any questions.

You are not required to respond to this notice about your patient however, you are welcome to contact the research team if you have any questions about the study

Yours sincerely,

Michaela Flynn
Section of Eating Disorders
Institute of Psychiatry, Psychology and Neuroscience
De Crespigny Park
SE5 8AF Email: michaela.flynn@kcl.ac.uk Phone: 020 7848 018

Appendix E.3. TANDEM Consent form for optional study about the treatment experience

ADULT CONSENT FORM PARTICIPANTS IN THE TANDEM STUDY: PARTICIPANT EXPERIENCE

Please complete this form after you have read the information sheet and listened to an explanation about the research.

Title of Study: A feasibility study of neuromodulation with attention bias modification training for binge eating disorder (TANDEM)

Optional Participant Experience Interview

Research Ethics Committee Reference:: 20/LO/0936 *IRAS ID: 284609*

Thank you for thinking about taking part in this research. The person organising the research must clearly explain the research to you and allow you to ask any questions you may have. If you have any questions, please discuss them with the researcher before deciding to participate. You will be given a copy of this consent form to keep and refer to at any time.

Please type your initials in the box below each point to indicate your consent.

- I have read and understood the participant information sheet (VX, XX/X/XXXX). I have had the opportunity to consider the information and ask questions.
- I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason, and without my medical care or 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 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 General Data Protection Regulation (GDPR, 2018). I understand that confidentiality and anonymity will be maintained, and it will not be possible to identify me in any publications
- I understand that any information collected about me will be kept confidential and that it will be stored in a secure and coded form accessible only to the project researchers.
- I understand that no information that could identify me will be used in any reports about this study and that any quotations used from interviews will be anonymised.
- I agree to have my interview with the researcher audio recorded. I understand that this recording is for research purposes. I know that I can stop the recording or having the recording destroyed if I want to.
- I agree to take part in the above study.

ADULT CONSENT FORM FOR PARTICIPANTS IN THE TANDEM STUDY: PARTICIPANT EXPERIENCE

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 the information included in this form and the participant information sheet and I understand what the study involves.

Signed:

Date:

Time:

Investigator's Statement:
I confirm that I have carefully explained the nature, demands and any foreseeable risks of the proposed research to the participant.

Signed:

Date:

Time:

Witness Statement
I confirm that procedures for informed consent have been followed in line with study protocol.

Signed:

Date:

Time:

Enquiries:
Michaela Flynn
Eating Disorders Research Group
Institute of Psychiatry, Psychology & Neuroscience,
De Crespigny Park,
London, SE5 8AF
Phone: 020 7848 0183 Email: michaela.flynn@kcl.ac.uk

Appendix E.4. Online consent form for the study of Cognitive Control Functions in Binge Eating Disorder and Obesity (CoCo).

Default Question Block

Consent Form for Partcipation in the CoCo Study: A study of Cognitive Control in Binge Eating Disorder and Obesity

Research Ethics Committee Reference Number: LRS-20/21-20873

Form Version 1, Date: 29th September 2020.

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.

As you have received this form, then you have told the researcher that you have read the participant information sheet about the CoCo study, you have listened to an explanation of the research, and you have been invited to ask any questions you may have about taking part. If you have further questions or require further

clarification, do not complete this form. Instead, as the research for more information.

I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason. I understand that I will be able to withdraw my data up until the 31st December 2021.

- ○ Yes
- ○ No

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.

- ○ Yes
- ○ No

I have read and understood the information sheet provided. I have had the opportunity to consider the information and ask questions.

- ○ Yes
- ○ No

I understand that I must not take part if I have any of the conditions listed in the exclusion criteria.

- ○ Yes
- ○ No

I know that if I would like to, I can contact the research team and request a written summary of findings of the study.

- ○ Yes
- ○ No

I am happy for my de-identified data (that is data that does not contain any identifiable information such as your name or contact information) to be archived and used for future related research.

- ○ Yes
- ○ No

OPTIONAL: I 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.

- ○ Yes
- ○ No

Participant Statement:

I have read this form and the corresponding Participant Information Sheet and had the study explained to me. I understand what the research study involves. I agree to take part in the above described study of cognitive control in binge eating disorder and obesity.

Please Type Your Full Name to Sign

Investigator's Statement:

In issuing access to this form I, Michaela Flynn, confirm that I have explained the study objectives and

procedures and given the participant the chance to ask questions and seek clarification.

Powered by Qualtrics

Appendix E.5. Equipment loan agreement for TANDEM participants

TANDEM STUDY: Brain Stimulation Equipment Return Agreement

Dear TANDEM participant,

For the duration of the treatment component of the TANDEM study (2-3 weeks) you will be provided with a transcranial direct current stimulator (HDC stimulator) and MindCap. These are essential for your participation and will be used only to enable you to carry out study-related tasks. After completing the study treatment, you will need to return the tablet to us, either in person or by courier service, paid for and organised by King's College London. While in your possession, please treat all study equipment with care and try your best to ensure that it is not damaged, lost or stolen.

This equipment is expensive, and our research funds are limited. Therefore, any loss of or damage to the stimulator is likely to affect the conduct of the study and may lead to your study participation being terminated prematurely. Thank you for your understanding!

Please complete the declaration below:

I, _____ (type your name), commit to looking after all study equipment to the best of my ability and to return it at the end of my study participation.

eSignature (type your name): _____

Date: _____

Co-Signed By Researcher:

eSignature (type your name): _____

Date: _____

Appendix F. Recruitment materials

Appendix F.1. Poster 1 advertising the TANDEM Study

Appendix F.2. Poster 2 advertising the TANDEM Study

Appendix F.3. Social media advertisement 1 for the TANDEM study

Appendix F.4. Social Media Advertisement 2 for the TANDEM Study

Appendix F.5. Poster advertising the CoCo study

CoCo

COGNITIVE CONTROL IN OBESITY AND BINGE EATING DISORDER

WHAT ARE WE DOING?

We are looking at if and how obese adults with and without BED differ in terms of the way they think.

WHO CAN TAKE PART?

Aged 18-60 years • Obese • Access to a computer with a webcam

WHAT WOULD I NEED TO DO?

- A 15-minute screening call
- An online assessment involving questionnaires and tasks lasting 2 hours

As a token of thanks for your time and efforts, you will receive £15 for taking part

Contact Michaela Flynn for more information:
michaela.flynn@kcl.ac.uk

KING'S College LONDON

REC Reference: LRS-2021-20873 Version 1 29th September 2020

Appendix F.6. Social media advertisement for the CoCo Study

Appendix G. Screening measures

Appendix G.1. General Health Screening Questionnaire for TANDEM

TANDEM Inclusion and Exclusion Criteria

Participant Initials: **Interview Method: Phone / Video Call**

Thank you for your interest in participating in the TANDEM study and for completing the study consent form. As you will know, the TANDEM study is looking at whether combining attention training with tDCS may benefit to people with binge eating. Today, I will be asking you some questions about your eating, your general health and medical history to check whether it is safe and suitable for you to take part. Before we begin, do you have any questions about the study or screening?

Are you happy for me to go ahead with the screening?

1. Have you ever been diagnosed with an eating disorder? …when were you diagnosed? … what is your current diagnosis/symptomatology?	**YES**	**NO**
2. Are you aged between 18 and 60? …what is your date of birth? _____	**YES**	**NO**
3. What is your dominant hand?	**LEFT**	**RIGHT**
4. What is your sex at birth?	**MALE**	**FEMALE**
5. How would you describe your gender? _____		

3. Have you been diagnosed with any of the following psychiatric disorders at any time in your life?

	YES	NO	WHEN
Depression	☐	☐	
Anxiety	☐	☐	
Schizophrenia or Psychosis	☐	☐	
Bipolar Disorder	☐	☐	
Drug/Alcohol Dependence Disorder	☐	☐	
Borderline Personality Disorder	☐	☐	
ADHD	☐	☐	

4. Have you been diagnosed with any <u>other</u> psychiatric disorder at any time in your life? If YES: • Which disorder(s): _____ • When were you diagnosed? _____	**YES**	**NO**
5. Are you currently taking any medication for a psychiatric condition?	**YES**	**NO**

If YES: • Which one(s) _____ • Since When: _____ • Dosage: _____ (SSRI ONLY) Has this dose been stable for the last 14 days?	**YES**	**NO**
5. Have you had any significant health problems in past 6 months? ….. if YES please provide more details about the nature and duration of the health problem? (Examples include diabetes, asthma, chronic pain, cardiovascular/heart problems?) _____ _____ _____	**YES**	**NO**
6. Are you currently taking any medication to manage a physical health condition? …if YES: • Which one(s) _____ • Since When: _____ • Dosage: _____	**YES**	**NO**
7. Have you ever been diagnosed with any developmental or neurological disorder? …if YES: • What is/was your diagnosis? _____ • When were you diagnosed? _____	**YES**	**NO**
8. Do you experience regular headaches, migraines, dizziness or fainting spells, double or blurred vision, numbness or tingling, or problems with balance? ….. if YES please provide more details: _____ _____ _____	**YES**	**NO**

9. Do you have any condition with specific needs or preferences that you would like to make us aware of? For example, some participants may have limited mobility or may not wish to remove a headscarf or have a skin condition on their scalp. …if YES please provide details: _____	**YES** **NO**
10. Do you suffer from any visual impairment or wear glasses to correct your vision? *Where glasses are needed ask whether the participant would be happy to wear these during their participation.*	**YES** **NO**
11. Diet (Please circle): None Vegetarian Vegan Other _____	
12. Do you have any food allergies or sensitivities? …if YES: • Which food(s)? _____	**YES** **NO**
13. Do you smoke cigarettes or use any form of nicotine replacement? …if YES and Cigarettes: • How many cigarettes do you smoke in an average day? _____ …if YES and Nicotine replacement: • What form of nicotine replacement do you use? _____ • Describe your daily usage (i.e., mL of Nicotine daily or similar if possible). _____	**YES** **NO**
14. Do you drink alcohol? …if YES, how much? _____ Days per week _____ Drinks per day OR _____ Units per average week	**YES** **NO**
15. Are you taking any other drugs, including weight loss pills or medication for another research study or clinical trial? Details: _____	**YES** **NO**

16. Do you take any recreational drugs? …if YES please provide details about type, frequency and most recent use.	**YES**	**NO**
15. Do you take the contraceptive pill or use another form of contraception? Please provide details. … if YES, please provide details:_____	**YES**	**NO**
16. Sufficient English Language Fluency (assessed based on conversation so far)	**YES**	**NO**

Appendix G.2. Eating Disorder Diagnostic Screen by Stice, Telch and Rizvi (2000)

	Not at all	*Slightly*		*Moderately*		*Extremely*	
1. Over the past 3 months have you felt fat?	0	1	2	3	4	5	6
2. Over the past 3 months have you had a definite fear that you might gain weight or become fat?	0	1	2	3	4	5	6
3. Over the past three months has your weight influenced how you think about (judge) yourself as a person?	0	1	2	3	4	5	6
4. Over the past 3 months 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 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**

IF NO GO TO Q. 11

6. During the times when you ate an unusually large amount of food, did you experience a loss of control (e.g. You may feel you couldn't stop eating or control what or how much you were eating)? **YES** **NO**

7. Can you tell me more about this? For example, what might you eat over what kind of time frame?

_____

_____

8. How many **DAYS per week** on average over the past 6 months have you eaten an unusually large amount of food and experienced a loss of control?

0 1 2 3 4 5 6 7

9. How many **TIMES per week** on average over the past 3 months have you eaten an unusually large amount of food and experienced a loss of control?

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

Other:_____

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10. During these episodes of overeating and loss of control did you…

a) Eat much more rapidly than normal?	**YES**	**NO**
b) Eat until you felt uncomfortably full?	**YES**	**NO**
c) Eat large amounts of food when you didn't feel physically hungry?	**YES**	**NO**
d) Eat alone because you were embarrassed by how much you were eating?	**YES**	**NO**
e) Feel disgusted with yourself, depressed, or very guilty after overeating?	**YES**	**NO**
f) Feel upset about your uncontrollable eating or resulting weight gain?	**YES**	**NO**

11. Have you ever made yourself vomit to prevent weight gain or counteract the effects of eating? **YES** **NO**

IF YES: How many **TIMES per week** on average over the past **3 months** made yourself vomit to prevent weight gain or counteract the effects of eating?

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

Other:_____

12. Have you ever used laxatives or diuretics to prevent weight gain or counteract the effects of overeating? **YES** **NO**

IF YES: How many **TIMES per week** on average over the past **3 months** have you used laxatives or diuretics to prevent weight gain or counteract the effects of eating?

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

Other:_____

13. Have you ever fasted to prevent weight gain or counteract the effects of eating? **YES** **NO**

IF YES: How many **DAYS per week** on average over the past **3 months** have you fasted (skipped at least 2 meals in a row) to prevent weight gain or counteract the effects of eating?

0 1 2 3 4 5 6 7

14. Have you exercised excessively specifically to counteract the effects of overeating? **YES** **NO**

IF YES: How many **TIMES per week** on average over the past 3 months have you engaged in excessive exercise specifically to counteract the effects of overeating episodes?

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

Other:_____

15. How much do you weigh? If you're not sure, please give your best guess. _____

16. How tall are you? _____

Biological Females Only: Over the past 3 months, have you missed any of your menstrual periods? If so, when was your last period? _____

Appendix G.3. tDCS Safety Screen by Keel (2000)

Please answer the following questions. 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
Do you have any metal in your head (outside the mouth) such as shrapnel, surgical clips, or fragments from welding or metalwork?	☐Yes	☐No
Do you have any implanted devices such as cardiac pacemakers, medical pumps, or intracardiac lines?	☐Yes	☐No
Do you suffer from frequent or severe headaches?	☐Yes	☐No
Have you ever had any other brain-related condition?	☐Yes	☐No
Have you ever had any illness that caused brain injury?	☐Yes	☐No
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:*

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Closing Statement:

That's the end of the screening. Before we wrap up, do you have any more questions? Thank you for taking the time to answer my questions. The next step is for me to review your responses and confirm whether you are safe and eligible to participate. I will contact you tomorrow to let you know, is there a good time for me to call?

Appendix H. Assessment outcome measures

Appendix H.1. Demographic Questionnaire

Demographic Information

Full Name:							
Date of Birth:	__ __ / __ __ /__ __ __ __						
Gender:							
Weight:							
Height:							
Occupation:							
Highest level of education obtained:	GSCE	AS levels	A levels	Undergrad	Masters	PhD	Other
Marital Status:	Single	Dating	Married	Spouse	Divorced	Widowed	Other
Ethnicity:	White		Asian		Black	Other: _____	
Number of children/dependents:							

Appendix H.2. Eating Disorder Examination Questionnaire (EDE-Q) by Fairburn and Beglin (2008)

Eating Disorder examination questionnaire (EDE-Q 6.0)

Instructions: The following questions are concerned with the past four weeks (28 days) only.

Please read each question carefully. Please answer all the questions. Thank you.

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

	ON HOW MANY OF THE PAST 28 DAYS ...	NO DAYS	1-5 DAYS	6-12 DAYS	13-15 DAYS	16-22 DAYS	23-27 DAYS	EVERY DAY
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 fla**t 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

PAGE 1/3 PLEASE GO TO THE NEXT PAGE

EDE-Q 6.0

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Eating Disorder examination questionnaire (EDE-Q 6.0)

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

Over the past four weeks (28 days)….

13	Over the past 28 days, how many **times** have you eaten what other people would regards 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. <u>Please note that for these questions the term "binge eating" means</u> eating what others would regard as an unusually large amount of food for the circumstances, accompanied by a sense of having lost control over eating.

		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

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Eating Disorder examination questionnaire (EDE-Q 6.0)

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).

	ON HOW MANY 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

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

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

If female: Over the past three to four months have you missed any menstrual periods?: YES ○ NO ○

If so, how many?: ○

Have you been taking the "pill"?: YES ○ NO ○

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THANK YOU

EDE-Q 6.0

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Appendix H.3. Fictional examples of subjective and objective binge episodes.

TANDEM study Assessment supporting document

Take as much time as you need to read through this sheet.
Please let the researcher know when you have finished reading.

Some questions ask about (1) eating what most people would regard as an unusually large amount of food and (2) feeling a sense of having lost control while eating.

1. An unusually large amount of food is something that *most* people would feel is more than a large meal.

2. A sense of having lost control while eating might be experienced as feeling driven or compelled to eat; not being able to stop eating once you have started; not being able to keep yourself from eating large amounts of certain kinds of food in the first place; or giving up on even trying to control your eating because you know that, no matter what, you are going to overeat.

Here are some examples: After work one evening, Dina ate two pieces of chicken, a 16-ounce package of frozen vegetables, three cups of rice, three fourths of a coffee cake, and a piece of fruit. This is an unusually large amount of food. While she ate, Dina felt completely out of control, ate more quickly than usual, and ate until she felt uncomfortably full. Afterwards, Dina was very upset about how much she had eaten, and said she felt depressed, guilty, and hated herself for giving in to the urge to binge.

Several times a week JoAnne ate lunch at McDonald's with two co-workers. Her usual order was a Big Mac, a fish fillet sandwich, two large orders of fries, and a large chocolate shake. This is an unusually large amount of food. Although she ate somewhat more than her friends did and knew she was eating a lot of high-fat food, she did not feel out of control while eating or feel upset afterwards about how much she had eaten.

For lunch one day, Joseph had a ham and cheese sandwich with mayonnaise on a roll, a small bag of potato chips, a candy bar, and a diet coke. Although this was a large meal, it was not unusually large. However, Joseph felt out of control because he had planned to have turkey on whole wheat with lettuce and tomato plus a piece of fruit for dessert, but changed his mind at the last minute while ordering his sandwich.

Carol ate two donuts someone brought to the office one morning. She had started a diet that day and planned to skip breakfast. Carol initially refused the donuts, but after everyone else had gone to a meeting she snuck into the break room and very quickly ate the donuts so no one would see her eating. She felt very guilty and ashamed afterwards and hated feeling so out of control of her eating, resolving to start dieting again the next day. Although Carol felt bad about eating the donuts, this was not an unusually large amount of food.

Dina and JoAnne ate an unusually large amount of food, but Joseph and Carol did not. Dina, Joseph, and Carol felt a loss of control while eating, but JoAnne did not. Of the four, **Dina is the only one who actually had a binge episode**, **which includes both** (1) eating an unusually large amount of food and (2) feeling a sense of having lost control while eating.

EDE-Q instruction, Taken from Goldfein et al. 2005

Appendix H.4. Food Craving Questionnaire - Trait Reduced Version by Cepeda-Benito, Gleaves, Williams & Erath (2000)

Below is a list of comments made by people about their eating habits. Please indicate how frequently these comments would be true for you in the last month. Please respond to each item as honestly as possible.

	Never	Rarely	Sometimes	Often	Usually	Always
When I crave something, I know I won't be able to stop eating once I start.	○	○	○	○	○	○
If I eat what I am craving, I often lose control and eat too much.	○	○	○	○	○	○
Food cravings invariably make me think of ways to get what I want to eat.	○	○	○	○	○	○
I feel like I have food on my mind.	○	○	○	○	○	○
I find myself preoccupied with food.	○	○	○	○	○	○
Whenever I have cravings, I find myself making plans to eat.	○	○	○	○	○	○
I crave foods when I feel bored, angry, or sad.	○	○	○	○	○	○
I have no will power to resist my food cravings.	○	○	○	○	○	○
Once I start eating, I have trouble stopping.	○	○	○	○	○	○
I can't stop thinking about eating no matter how hard I try.	○	○	○	○	○	○

	Never	Rarely	Sometimes	Often	Usually	Always
If I give in to a food craving, all control is lost.	○	○	○	○	○	○
Whenever I have a food craving, I keep on thinking about eating until I actually eat the food.	○	○	○	○	○	○
If I am craving something, thoughts of eating it consume me.	○	○	○	○	○	○
My emotions often make me want to eat.	○	○	○	○	○	○
It is hard for me to resist the temptation to eat appetising foods that are in my reach.	○	○	○	○	○	○

Appendix H.5. Depression, Anxiety, Stress Scale – 21 item version by Lovibond & Lovibond (1996)

$DASS_{21}$

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 are 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 (e.g. 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 thing	0☐	1☐	2☐	3☐
6	I tended to over-react to situations	0☐	1☐	2☐	3☐
7	I experienced trembling (e.g. 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 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 I was rather touchy	0☐	1☐	2☐	3☐
19	I was aware of the action of my heart in the absence of physical exertion (e.g. 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 H.6. Difficulties with Emotion Regulation Scale (DERS) by Gratz and Roemer (2004)

Please indicate how often the following statements apply to you.

	(Almost) Never	Sometimes	Regularly	Often	Almost Always
I have difficulty making sense out of my feelings.	○	○	○	○	○
I am confused about how I feel.	○	○	○	○	○
When I am upset, I have difficulty getting work done.	○	○	○	○	○
When I am upset, I become out of control.	○	○	○	○	○
When I am upset, I believe that I will remain that way for a long time.	○	○	○	○	○
When I am upset, I believe that I'll end up feeling very depressed.	○	○	○	○	○
When I am upset, I have difficulty focusing on other things.	○	○	○	○	○
When I am upset, I feel out of control.	○	○	○	○	○

| | (Almost) Never | Sometimes | Regularly | Often | Almost Always |

When I am upset, I feel ashamed with myself for feeling that way.	○	○	○	○	○
When I am upset, I feel like I am weak.	○	○	○	○	○
When I am upset, I have difficulty controlling my behaviors.	○	○	○	○	○
When I am upset, I believe that there is nothing I can do to make myself feel better.	○	○	○	○	○
When I am upset, I become irritated with myself for feeling that way.	○	○	○	○	○
When I am upset, I start to feel very bad about myself.	○	○	○	○	○
When I am upset, I have difficulty thinking about anything else.	○	○	○	○	○
When I am upset, my emotions feel overwhelming.	○	○	○	○	○

Clinical Impairment Assessment

Appendix H.7. Clinical Impairment Assessment by Bohn and Fairburn (2008)

CIA version 3.0 (Copyright Bohn and Fairburn, 2008)

INSTRUCTIONS
Please place an 'X' in the column which best describes how your eating habits, exercising, or feelings about your eating, shape or weight have affected your life OVER THE PAST 28 DAYS. Thank you.

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

Appendix H.8. Visual Analogue Scales (VAS) for Current Binge Eating Disorder Symptoms

Core BED VAS Measures

1. Please mark the following line at the point that most accurately reflects your current **urge to binge eat.**

   No urge to binge at all _____ Extremely strong urge to binge

2. Please mark the following line at the point that most accurately reflects your **craving for food**

   No craving for food at all _____ Extremely strong craving for food

3. Please mark the following line at the point that most accurately reflects your current **urge to eat**

   No urge to eat at all _____ Extremely strong urge to eat

4. Please mark the following line at the point that most accurately reflects your current **hunger**

   No hunger at all _____ Extremely strong hunger

5. Please mark the following line at the point that most accurately reflects the extent to which **you feel full**

   Not feeling full at all _____ Feeling extremely full

6. Please mark the following line at the point that most accurately reflects your current **level of tension**

   Not feeling tense at all _____ Feeling extremely tense

7. Please mark the following line at the point that most accurately reflects your current **level of stress**

   Not feeling stressed at all _____ Feeling extremely stressed

8. Please mark the following line at the point that most accurately reflects your current **level of anxiety**

Not feeling anxious at all	———————————————	Feeling extremely anxious

9. Please mark the following line at the point that most accurately reflects the extent to which you are **feeling low**

Not feeling low at all	———————————————	Feeling extremely low

Appendix H.9. Visual Analogue Scales (VAS) for current psychopathology

Related VAS Measures

1. Please mark the following line at the point that most accurately reflects your current **level of tension**

   Not feeling tense at all _____ Feeling extremely tense

2. Please mark the following line at the point that most accurately reflects your current **level of stress**

   Not feeling stressed at all _____ Feeling extremely stressed

3. Please mark the following line at the point that most accurately reflects your current **level of anxiety**

   Not feeling anxious at all _____ Feeling extremely anxious

4. Please mark the following line at the point that most accurately reflects the extent to which you are **feeling low**

   Not feeling low at all _____ Feeling extremely low

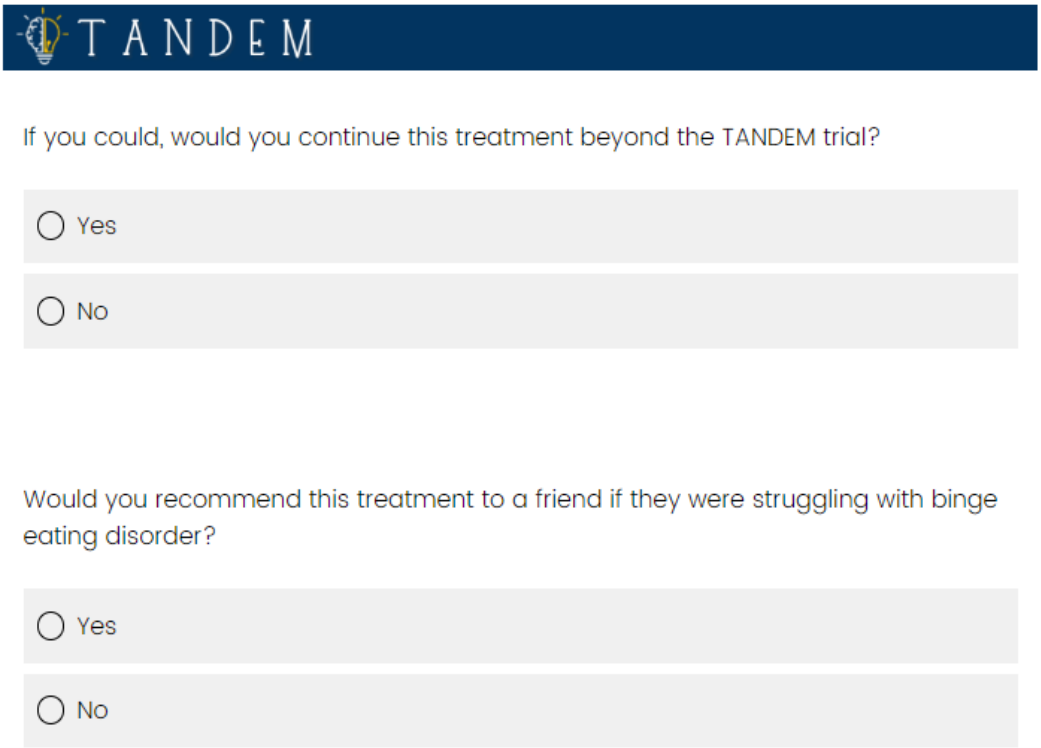
Appendix H.10. Visual Analogue Scales (VAS) for tDCS related discomfort

tDCS VAS Measures

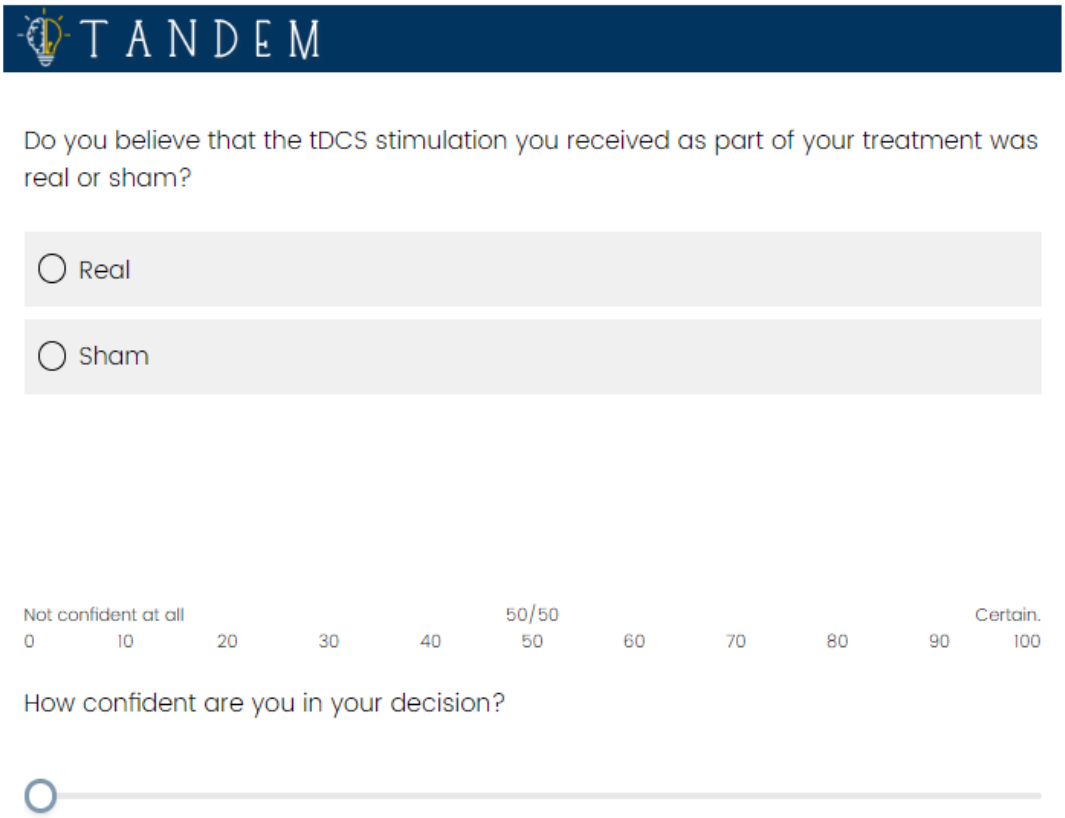
1. Please mark the following line at the point that most accurately reflects the **discomfort you experienced during tDCS.**

No Discomfort ——————————————— Extreme Discomfort

Appendix H.11. Assessment of intervention acceptability



Appendix H.12. Assessment of Blinding Success



Appendix H.13. Topic guided for treatment experience interview

TANDEM Study Treatment Experience Interview Prompts

Affective attitude:

1. Why did you want to take part in this study?
2. What, in your view, may be a reason for people not to take part in this study?
3. How did you feel about taking part in a study which involved brain stimulation?
4. Did you have any concerns about taking part in this study?
5. Did you discuss your plan to take part with anyone i.e. loved one or healthcare professional prior to reaching a decision?
6. Prior to taking part, did you have a preference for one of the interventions?

Ethicality:

1. To what extent was [tDCS with attention training/attention training] a suitable treatment option for you?
2. Have you had any prior treatment for you eating difficulties? If so, how does [tDCS with attention training/attention training] compare to treatment you received previously? What suits you best?

Perceived Effectiveness:

1. Do you view [tDCS with attention training/attention training] as an effective treatment option for binge eating disorder?
2. How did you feel about receiving a treatment intervention at home? Would you have preferred to complete the treatment in a different setting? PROMPT: Do you feel completing the intervention at home impacted on its effectiveness?
3. Have you noticed any changes in yourself, positive or negative, since completing treatment?
   PROMPT: mood, food cravings, binge frequency, feelings about eating, food consumption, physical wellbeing, quality of life, daily functioning, etc.
4. Have others noticed a change in you since completing treatment? i.e. friends, family, GP, therapist

Burden:

1. Was there anything that got in the way of treatment for you?
2. What, if anything, do you feel may make it challenging or burdensome for others to complete this intervention?
3. What were your thoughts about the safety of doing brain stimulation at home with remote supervision?
4. What was your experience of the brain stimulation? PROMPT: discomfort, tolerability, sensations
5. Did you experience any side effects that may be related to the brain stimulation? PROMPT: headaches, nausea, dizziness, fatigue, etc

Opportunity Cost:

1. Did you have to make sacrifices in order to attend the treatment sessions?
2. In your view, is there anything we could do to make the intervention more accessible or more accommodating?
3. Did you feel your attendance was affected by being at home?
4. How did you find the frequency and duration of treatment sessions? PROMPT: too long, too short, too many, not enough.

Intervention coherence:

1. During treatment, was it clear to you how the intervention worked? Can you tell me a little bit of what you remember?
2. How did the researchers think the intervention could influence your symptoms?
3. How important is it for you that you understand how an intervention works?

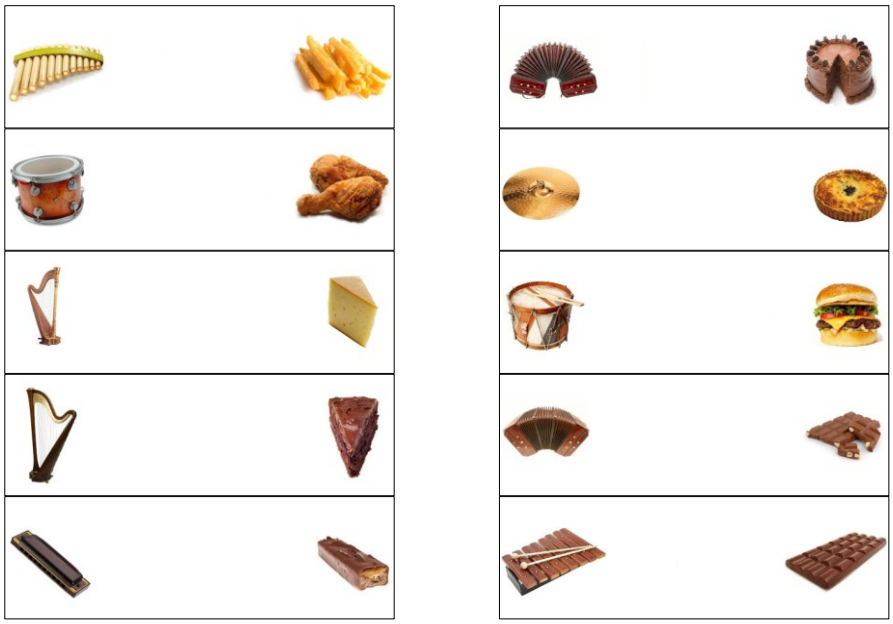
Self-efficacy:

1. Did you feel capable of leading your own treatment at home?
2. Did you feel that you were sufficiently trained to use the equipment independently?
3. How important was the role of the research supervisor to you? PROMPT: Did their presence affect your attendance and/or engagement with the treatment? Do you feel you would be able to complete treatment if they had not been there?

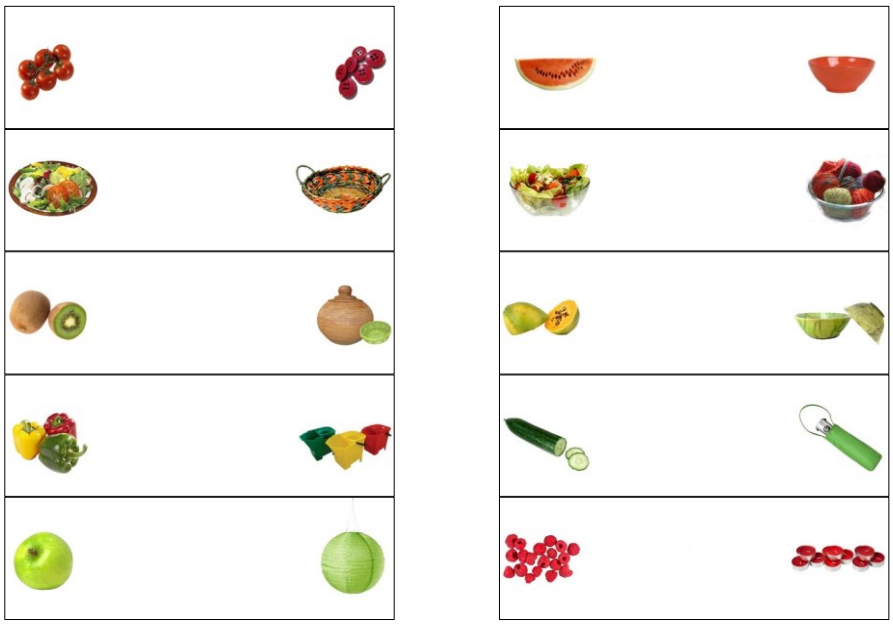
Is there anything else you'd like to add that may help us to understand your experience receiving treatment or your ideas for the future?

Appendix H.14. High- and Low-Calorie Food Stimuli for Visual Probe Task

High Calorie:



Low Calorie:



Appendix I. Intervention materials

Appendix I.1. tDCS self-administration safety checklist

TANDEM tDCS Self-Administration Checklist

Assessor	Participant ID	Date

Head and MindCap Preparation	Satisfactory / Comments
Parts hair to expose stimulation site and cleans skin with alcohol.	
Checks the skin for signs of redness, cuts, grazes or pimples.	
Checks the MindCap electrodes for signs of damage or wear and tear.	
Soaks the electrode sponges in a bath of saline solution for 15 minutes.	
Attaches the leads to the correct clips on the outside of the cap, and secures the leads using the clip at the back of the cap.	
Inserts the electrode sponges on the inside of the cap. Attaches the electrode to the corresponding lead.	
Places the cap on their head. Adjusts the chin strap closure and the rear closure for good fit.	

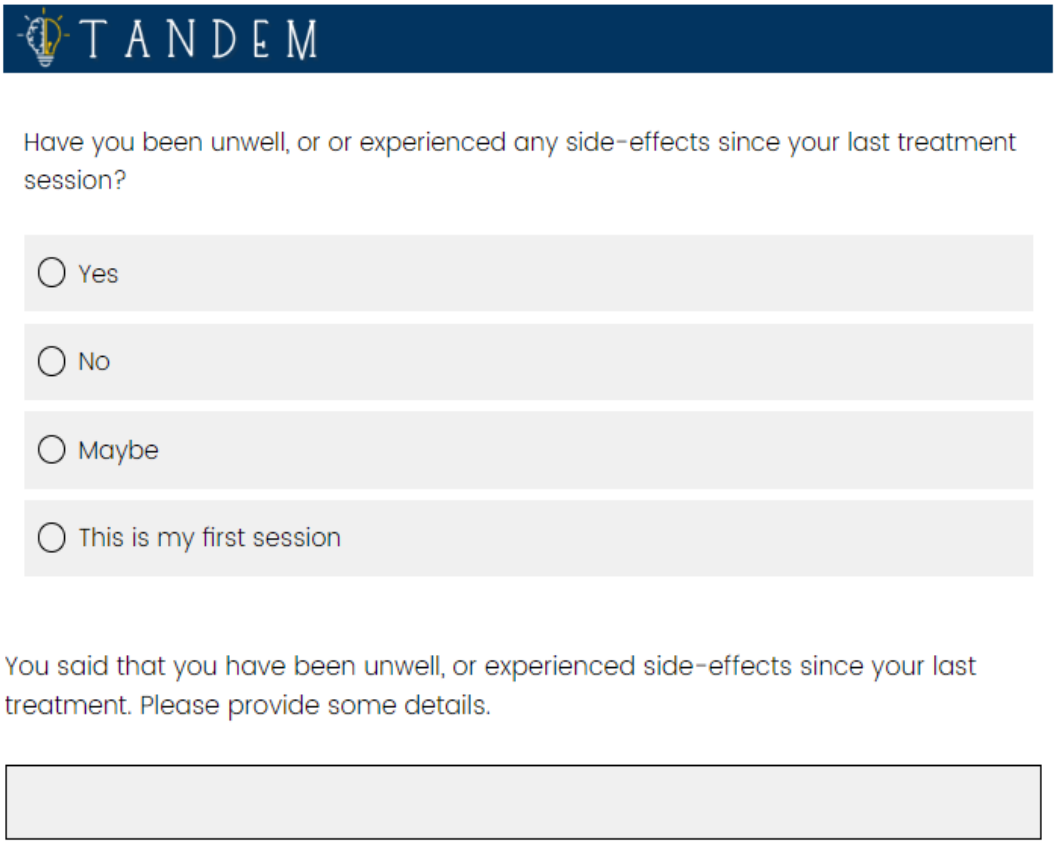
Machine Preparation and Stimulation	Satisfactory / Comments
Correctly connects the electrode leads to the stimulator. The red wire must be inserted into the red slot and the black wire must be inserted into the black slot.	
Understands the electrode contact quality message and demonstrates that they can adjust improve electrode contact as needed.	
Correctly enter activation code to initiate stimulation	

During Stimulation	Satisfactory / Comments
Demonstrates an understanding of the importance of avoiding distractions or interruptions for he period of stimulation.	
Can monitor the quality of electrode contact during stimulation.	

After Stimulation	Satisfactory / Comments
Gently remove sponges from the MindCap and clean them with water.	
Recharge / Replace batteries if required.	

Outcome		
Participant was assessed to be competent at delivering tDCS	YES	NO

Appendix I.2. Within-session assessment of adverse side effects



Appendix I.3. Within-session measure of objective binge eating

Appendix J. COVID-19 Impact Statement: Supporting Materials

Appendix J.1. Protocol for a Theta Burst Stimulation study in Binge Eating Disorder (BITE)

1. PROTOCOL FULL TITLE

Protocol Short Title/ Acronym: Theta burst stimulation in binge eating disorder (BITE)

Trial Identifiers

NCT Numbers:	NCT04129970 and NCT04130906		
REC Number:			
UKCRN Number:			
Protocol Version Number:	6.0	Date:	17/04/2020

(Co) Sponsor(s)

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2. Study Synopsis

TITLE OF CLINICAL TRIAL:	BITE: An integrated feasibility trial and case series of theta burst simulation in binge eating disorder
Protocol Short Title/ Acronym:	Theta Burst Stimulation in Binge Eating Disorder (BITE)
Study Phase If Not Mentioned in Title:	N/A
Sponsor Name:	King's College London
Chief Investigator:	Professor Ulrike Schmidt
NCT Number:	NCT04129970 and NCT04130906
REC Number:	TBA
Medical Condition or Disease Under Investigation:	Binge eating disorder
Purpose of Clinical Trial:	This study aims to assess the feasibility and effects of neuro-navigated intermittent theta burst stimulation (iTBS) delivered to the left dorsolateral prefrontal cortex (DLPFC) in an adolescent and adult population with binge eating disorder (BED), and to acquire key information needed for the development of a future large-scale randomised sham-controlled trial (RCT). This trial is conducted in the UK.
Primary Objective:	The primary objective of this integrated study is to establish the feasibility of conducting a large-scale RCT of iTBS in people with BED by assessing recruitment, attendance, retention rates, safety and intervention tolerance.
Secondary Objective(s):	Secondary objectives are to investigate whether there may be short- and longer-term therapeutic effects associated with iTBS; specifically, the trail aims to assess whether iTBS influences craving, binge eating, weight, and mood in people with BED.

	Further, the trial aims to investigate the neurocognitive mechanisms underlying treatment response.
Trial Design:	Integrated proof-of-concept double-blind sham-controlled RCT and a non-randomised feasibility case-series
Endpoints:	In the single session RCT, core BED symptom severity will be assessed prior to iTBS, post-iTBS and at 24-hour follow-up. In the case-series, core BED symptom severity, craving for food, negative affect and physical health will be assessed prior to iTBS then again following 20-sessions of iTBS and at 3-month follow up.
Sample Size:	68 individuals who meet diagnostic criteria for BED will participate in the single-session RCT. 22 individuals from the RCT will participate in the case series.
Summary of Eligibility Criteria:	Right handed male and female individuals (aged 13-60) will be eligible if they meet DSM-5 criteria for full-syndrome BED and they are overweight or obese according to World Health Organisation (WHO) criteria (BMI>25 kg/m^2 for adults, and a weight-for-height greater than 2 standard deviations above the median for adolescents). Exclusion criteria include: All known contraindications to MRI and TBS (assessed using TMS and MRI safety screening questionnaires); pregnancy (or suspected pregnancy); history of neurological disease and/or seizure; having any metallic implants anywhere in the head or body; history of head or eye injury; significant health problems in the previous six months; lifetime diagnosis of substance dependence, psychosis, bipolar disorder, borderline personality disorder; other primary psychiatric disorder requiring treatment in its own right; taking psychotropic medication other than a stable dosage of selective serotonin reuptake inhibitors (SSRI) for at least 14 days prior to study enrollment; alcohol consumption exceeding 14 units per week; cigarette consumption or nicotine replacement exceeding >15 cigarettes daily or equivalent.
Intervention (Description, frequency, details of delivery)	In iTBS, an electrical current is passed through a coil placed on the scalp. This electrical current generates a magnetic field, which is then pulsed in triplet-bursts over a target region on the scull, altering cortical excitability in the structures immediately below. Prior to receiving iTBS, all participants will undergo a structural magnetic resonance imaging (MRI) scan to enable localisation of the left DLPFC (using Brainsight™ neuro-navigation software). To determine stimulation intensity, resting motor threshold (rMT) will be determined for all participants using the Motor Evoked Potential Method. Intermittent TBS will be delivered at 80% of rMT using standard stimulation parameters; triplet-bursts delivered at 50 Hz with an inter-burst interval of 200 ms. Each train will last 2 seconds and consists of 10 triplet-bursts (30 pulses). A complete TBS session will involve 10 iTBS trains repeated every 10 seconds for 190 seconds, with a total number of 600 pulses delivered during the session. Participants in the RCT will receive a single session of either real or sham iTBS (600 pulses). Participants in the therapeutic case series will receive 20 sessions of real iTBS over a 4-week period (12,000 pulses). All procedures and stimulation parameters are in line with current safety and application guidelines for TMS.

Comparator Intervention:	Resting motor threshold will be determined or all participants using the Motor Evoked Potential Method. Sham stimulation will be delivered at 80% of rMT using the same stimulation parameters as for the active condition however, a Magstim® Sham coil will be used.
Maximum Duration of Treatment of a Subject:	4 weeks
Version and Date of Final Protocol:	Version 1; 18th September 2019
Version and Date of Protocol Amendments:	

3. Revision History

Document ID - (Document Title) revision X. Y	Description of changes from previous revision	Effective Date
Protocol Version 2	Study descriptions were updated to make the relationship between the two studies (the single session RCT and Case Series more clear to the reader).	
Protocol Version 3	Eligibility criteria has been updated to reflect changes to IRAS. We have elaborated on guidance for the safe delivery of TBS and TMS in adults, adolescents and children as recommended.	
Protocol Version 5	Changes made in response to feedback from North West Preston REC	

4. Protocol Contents

5. Background & Rationale

Binge eating disorder (BED) is a common and disabling eating disorder (ED) which presents substantial disease burden. The population prevalence of BED is between 1-3% [1, 2], with peak onset during developmentally sensitive adolescent and emerging adulthood years [3, 4]. BED is characterised by recurrent, psychologically distressing, episodes of binge eating during which the person consumes an unusually large amount of food over a short time-period and experiences a loss of control over-eating behaviour. These episodes occur in the absence of compensatory behaviours to avoid weight gain [5]. Amongst individuals with BED, psychiatric comorbidities are common; nearly 80% of those diagnosed will suffer from another mood, anxiety, substance use or eating disorder during their lifetime [1]. Similarly, incidence of risky substance use, suicidal ideation and self-harm are elevated in this group [2, 6]. BED is also associated with current, and the future development of, obesity; adult data from the World Health Organisation suggest that 30.7% of individuals with BED are overweight, and a further 36.2% are obese [1]. The combined presentation of BED and obesity is associated with debilitating obesity-related medical complications and severe psychiatric comorbidity, elevated functional impairment, and poorer outcomes from conventional treatment [7-9].

Talking therapies, most notably cognitive behaviour therapy, are presently recommended for the treatment of BED for both adolescents and adults. However, outcomes from treatment are inadequate. A recent meta-analysis concluded that only 45-54% of patients abstain from binging following conventional treatment and that drop-out rates are high (17-30%). Further, it was noted that very few rigorous randomised control trials (RCTs) have been conducted in adolescent patient groups and that data relating to long-term outcomes and relapse rates were lacking [10]. Similarly, although pharmacological interventions, such as lisdexamfetamine, reduce the frequency of binge eating behaviour, they are only moderately effective in supporting long-term weight management and adverse side-effects are common [11]. Where first-line interventions have been ineffective, and obesity is severe bariatric surgery is recommended. Up to 65% of surgery candidates meet the criteria for BED [12]. However, outcomes from bariatric surgery are markedly poorer for individuals with BED, with inferior weight loss reported in both adults and adolescents [13, 14], and pervasive post-operative mental health difficulties prevalent amongst adolescents [15]. As a result, novel treatment options which both facilitate weight loss and address the mechanisms driving binge-eating behaviour are urgently needed to improve outcomes for this patient population.

While the cause for overweight and obesity is well-known (i.e., an individual's intake of food exceeds the homeostatic energy needs), the mechanisms underlying pathological eating behaviour are far more complex. Fortunately, the neurobiological basis for BED is gradually becoming clearer. A comprehensive review by Kessler et al. [16] summarised the data available from neuroimaging studies conducted in this population and concluded that individuals with BED show increased impulsivity, compulsivity, and altered reward sensitivity, as well as enhanced attentional biases for food and impaired cognitive function. These behaviours appear to be related to aberrant functioning of the ventral striatum, which underlies goal-seeking behaviour, motivation, and reward sensitivity; the dorsal striatum, which underlies habitual and compulsive behaviours; the prefrontal cortex, which underlies executive function; and the insula which underlies interoception, decision making, taste perception and food regulation. Further, several neurotransmitter systems have been implicated, most notably mesolimbic dopaminergic systems. Clinically, this is reflected in abnormal reward processing, craving, diminished cognitive control, compromised emotion regulation, and high levels of negative affect. Importantly, the altered functioning reported in BED bares close resemblance to that reported in simple obesity (i.e., obesity without BED), with evidence to suggest that impairments are further exaggerated by BED. As such, it has been suggested that obese individuals with BED represent a distinct neurobiological phenotype within the obesity spectrum, which may be characterised by increased impulsivity [17], exaggerated reward sensitivity [18], and difficulties with emotion regulation [19].

Neurocognitive theories of eating behaviour generally associate the dysregulation of food intake with alterations within either the reward system or cognitive control system, or both. A recent and comprehensive meta-analysis by Devoto et al. [20] concluded that the Incentive Sensitisation Theory of Obesity proposed by Berridge [21] provides a particularly robust explanation for obesogenic behaviour, which may also be informative for BED. Incentive Sensitisation Theory conceptualises eating behaviour in light of the neural mechanisms that generate "liking" and "wanting" for food and considers how these may be modulated by hunger and satiety. Specifically, this model proposes that normal hunger acts as a physiological "drive" signal to magnify the incentive "wanting" and hedonic "liking" triggered by tasty foods and their associated cues, whereas satiety dampens the impact of these stimuli. In the case of obesity, individuals with higher reactivity in mesolimbic circuits may have higher incentive salience for foods, and possibly higher hedonic

impact, leading to greater “wanting”, and perhaps “liking”, to eat. In addition, this theory outlines a critical role for stress; highlighting that stress, both positive and aversive, may be associated with a neural response promoting the consumption of highly palatable, “soothing” food. This assertion is consistent with emotion regulation models for BED which propose that, in the context of BED, negative emotions act as a trigger for binge eating, and that binge eating may relieve negative emotions in the short-term (while binging) or long-term (after binging) [22]. In line with this, it may be hypothesised that remission from BED is associated with changes to the reward-cognition balance; specifically, remission may require the facilitation of increased cognitive control (and therefore improved self-regulation) and the suppression of reward-related mechanisms driving craving/binge-eating [23].

In recent years, there has been a surge of interest in exploring the potential applications for non-invasive brain stimulation (NIBS) techniques in the investigation and treatment of EDs, and there are several key reasons why NIBS techniques may be particularly efficacious in this population. Firstly, NIBS techniques allow for precise intervention which targets cortical regions or networks known to be implicated in psychiatric illness. As such, NIBS techniques may provide an avenue for modifying the automatic cognitive processes associated with disordered eating by directly targeting the neural mechanisms driving pathology. Secondly, their mechanisms of action differ from those of pharmacotherapy, and thus they offer fresh hope to those who fail to respond to medication. Thirdly, with increasing use of electronic and mobile devices that interface/interact with the human body (e.g. smartphones, watches with sensors and apps that monitor individuals’ vital characteristics and behaviour), use of medical technologies that interact with the central nervous system may also be more acceptable now than in previous years. Fourth, NIBS have been shown to improve cognition and a range of non-specific symptoms (e.g. stress) in healthy populations, and to be efficacious in the treatment of related psychiatric disorders, such as depression and addiction.

Transcranial magnetic stimulation (TMS) techniques are a family of NIBS techniques designed to modulate cortical excitability via the application of magnetic pulses. Repetitive TMS (rTMS), which involves the application of multiple pulses over a specified time-frame, has been used extensively to up- or down-regulate cortical excitability with the objective of 1) exploring the functional relationship between specific cortical regions, 2) achieving lasting changes in neural functioning, and 3) assessing neuroplasticity [24]. While the precise mechanisms by which TMS alters neural functioning remain unclear, emerging evidence from experimental studies in neurophysiology appear to indicate that that TMS may lead to neuroplastic changes in the brain (e.g., recent work by Selby et al. [25]). In medicine, rTMS is being harnessed for the treatment of psychiatric disorders, most notably major depression; excitatory rTMS targeting the left dorsolateral prefrontal cortex (DLPFC) is a well-established evidence-based treatment for major depressive disorder endorsed by the National Institute for Health and Care Excellence (NICE; 2015) and the US Food and Drug Administration (FDA; 2008). Intermittent theta burst stimulation (iTBS) is a novel variant of rTMS which uses patterned (triplet-burst) stimulation to produce excitatory effects comparable to rTMS which has also received considerable interest within psychiatry [27]. The main attraction of iTBS is the speed of application; a full iTBS session can be delivered in ~3 minutes, as opposed ~40 minutes for a standard excitatory rTMS session [28, 29]. Further, iTBS also utilises a lower stimulation intensity than conventional rTMS and appears to have an equivalent, if not superior, safety and side effect profile [30]. To date, research has found iTBS to be associated with improvement in clinical symptoms in depression [29, 31] and obsessive compulsive disorder [32], with some evidence to suggest benefit for disorders of addiction [33] though further research is needed. As such, iTBS is emerging as a potential treatment for psychiatric disorders that may be provide a cost-effective, efficient, and potentially safer, alternative to standard rTMS.

In light of the evidence to suggest that rTMS and its variants may alleviate the symptoms of psychiatric disorder, there is substantial interest in investigating their application to disorders of eating behaviour. While no study to date has used iTBS in EDs, obesity or “strong cravers”, several studies assessing outcomes following standard rTMS protocols targeting the prefrontal cortex have reported promising, albeit mixed, results. In healthy volunteers reporting “strong craving for food”, it was demonstrated that a single session of high-frequency rTMS applied to the left DLPFC inhibited food craving, compared to sham [34]. However, this finding was not replicated in a similar study by Barth et al. [35] which used a lower stimulator intensity than the previous trial. Further, localisation of the DLPFC was not MRI-guided and may not have been accurate. This may have contributed to the negative findings. Interestingly, one very recent study in healthy women by Lowe et al. [36] assessed the effects of inhibitory TBS (continuous theta burst stimulation; cTBS) targeting the left DLPFC on snack food consumption and craving. The authors revealed a reliable effect of cTBS on food consumption and craving; it was reported that following a single-session of real, as opposed to sham, cTBS participants selectively ingested significantly more calories from palatable, high-calorie snack foods and reported elevated craving. Further, concurrent EEG data provided evidence for a causal role of the

left DLPFC in the modulation of calorie dense food consumption and craving for food, providing a strong rationale for left DLPFC stimulation in populations with binge-eating pathology.

In bulimia nervosa (BN), an ED characterised by objective binge-eating and compensatory purging behaviour, several studies have demonstrated therapeutic benefit following excitatory rTMS targeting the dorsolateral and dorsomedial areas of the prefrontal cortex [37-40]. In a proof-of-concept study, Van den Eynde [37] reported a short-term reduction in craving and objective binge-eating following a single session of high-frequency rTMS to the left DLPFC. This finding was replicated in a later study by Sutoh et al. [38] which combined rTMS with near-infrared spectroscopy. Sutoh et al. reported that the observed reduction in craving following rTMS may be associated with a significant decrease in cerebral oxygenation of the left DLPFC. A case study describing a female with both refractory BN and comorbid depression also reported improvement in binge eating, purging, and depressive symptoms following a course of 20 sessions of rTMS to the dorsomedial PFC [39]. Finally, in a randomised, sham-controlled trial involving participants with anorexia nervosa and BN, robust improvement in bingeing and purging was reported following excitatory rTMS targeting the dorsomedial PFC [40]. In contrast, two trials investigating the effects of multiple sessions of rTMS on craving, binge-eating and purging behaviour in BN have reported a lack of clinical utility for rTMS in BN [41, 42]. However, in both cases the authors highlight that methodological issues and lack of power are likely to have influenced their findings.

Studies of rTMS in patients with BED are lacking though preliminary results are promising. One case study of a young female with refractory BED and comorbid depression reported clinical improvement following rTMS treatment. The study reported that twenty sessions of high-frequency rTMS targeting the left DLPFC led to a reduction in binge frequency, as well a significant improvement in depressive symptoms [43]. This finding is complemented by those from recent randomised control trials assessing the effects of excitatory rTMS on food intake and weight loss in obesity [44, 45]. Kim et al. reported a reduction in food-intake and significant weight loss following 20 sessions of excitatory rTMS targeting the left DLPFC [44]. Similarly, Alvarado-Reynoso and Ambriz-Tututi (2019) found that excitatory rTMS, combined with a low-carbohydrate diet, resulted in significant weight loss and reductions in anxiety and food craving.

As such, the available evidence suggests that further investigation into the use of rTMS protocols, including iTBS, in patients with BED may be fruitful. Similarly, evidence from neurobiological studies and previous rTMS investigations support the hypothesis that enhancing DLPFC activity via iTBS may alter the reward–cognition balance towards the facilitation of cognitive control and the suppression of reward-related mechanisms driving food craving/overeating. The present integrated trial, comprising of a proof-of-concept RCT and case series, aims to assess the feasibility and acceptability of iTBS in the clinical population with BED, and assess the short (i.e., 24-hour) and long-term (i.e., 3 month) efficacy of iTBS in changing core symptoms of BED. This will provide valuable data which will inform the development of a large-scale clinical trial in the future.

Potential Risks

Theta Burst Stimulation:

Transcranial magnetic stimulation (TMS) techniques, including TBS, are considered safe when applied within the recommended guidelines [46]. Guidance for the safe use of rTMS in adults are readily available, however, child and adolescent specific guidance are lacking. Presently, when using rTMS in children and adolescents, the literature recommends close adherence to the most recent adult safety guidelines and surveillance of adverse events through surveys and assessments on a session-basis [47]. In the current study, a standard stimulation protocol proposed by Huang et al (2005) will be used; participants will be given a triplet-burst of 50Hz, 2s on and 8 seconds off (600 pulses per second) for a total duration of 3 minutes and 9 seconds to the left dorsolateral prefrontal cortex (DLPFC). This is a frontal area of the brain involved in higher cognitive functions. The protocol to be used delivers TBS within the parameters recommended for safe use in adults [30]. In line with the recommendations for using TBS in child and adolescent participants mentioned above, TBS related discomfort and adverse events since the previous session will be assessed at each stimulation session.

TMS and TBS have been safely delivered to adults [48]. TMS and TBS have also both been safely delivered to children as young as 3 years old (~4000 children) and 6 years old (130 children) respectively [47]. Risk to children and adolescents from TBS has been reported to be equivalent to that reported in adult populations. The most commonly reported side effect of TBS experienced by both adults and children/adolescents is

transient headache and neck pain; these mild adverse events are reported in 3% of adults following TBS [30] and 9.78% of children/adolescents [47]. The most serious side effect is seizure; however, this is very rare, and this has been reported in 0.02% of adults [30] and 0.14% of children/adolescents [47].

To ensure participant safety, participants will fulfil the TMS safety screening questionnaire before study enrolment to check for any contraindications to TMS/TBS (e.g., history of seizure, neurological disease, or metallic body implants). All that report contraindications will be excluded from the study for their safety.

MRI: MRI is a widely used research and clinical tool. It is a non-invasive technique that uses volumetric scan sequences to calculate volumes of tissue in the brain and provide static anatomical information. The use of a strong magnetic field poses an important risk to participants when ferromagnetic objects are within the vicinity of the magnetic field. However, well established protocols are in place to manage this risk. MRI contraindications will be screened for prior to the scanning sessions and will be checked by a clinical radiologist. Any participant presenting with an MRI contraindication (including metal in the body, implanted devices, or aneurysm clips) will be excluded from participation on this basis.

Participants bodies may become heated by the radiofrequency (RF) emitted during the scan. To ensure safety, the MRI scanner has an inbuilt mechanism to control for thermoregulation due to RF energy. Participants are weighed before the scan and this information is entered when setting up the scanning session. The scanner uses this data to calculate the Specific Absorption Rate (SAR) for the participant and an inbuilt mechanism prevents scanning (i.e., RF exposure) above a calculated safety threshold. The MRI machine is loud and needs to be kept cool. Participants will be provided with ear protectors and a blanket to minimise discomfort. To minimise discomfort during MRI scanning, participants will be invited to attend an optional session in a mock MRI scanner prior to starting the trial. This session will allow participants to familiarise themselves with the scanning environment and procedures and enable them to make a more informed decision about their participation.

Although MRI scans are conducted for research purposes, there is a chance of incidental findings of clinical relevance (e.g., tumours or lesions). In the event of an incidental finding, the radiologist performing the scan will notify the participants GP, who will then be responsible for informing the participant and taking further action. As the researcher will not be directly informed of these results, at the time of obtaining informed consent participants will be encouraged to review their participation in the study with their GP if they are notified of an incidental finding in their pre-MRI scan.

Questionnaire Measures and Cognitive Tasks: There are no risks associated with the administration of the questionnaire measures and cognitive tasks to be completed in this study. For example, study measures of depression, anxiety and stress (DASS-21; 63) and eating disorder pathology (EDE-Q; 60) have robust empirical support for their use in both adolescents and adults.

Rationale for intervention parameters

Treatment parameters for rTMS and iTBS are yet to be standardised for psychiatric research, and the optimal parameters for therapeutic benefit remain unknown. As such, the parameters to be used in the present investigation are based on those established for the use of iTBS in neurophysiology [27] and those used in studies of major depression [29]. The choice of stimulation sight is both pragmatic and hypothesis driven. Neuroimaging research in BED and obesity, as well as other related EDs, show diminished activation of the DLPFC. It is hypothesised that up-regulation of the left DLPFC may alter the reward–cognition balance towards the facilitation of cognitive control and the suppression of reward-related mechanisms driving food craving/overeating. This decision is consistent with that of previous rTMS studies in populations with elevated food craving, obesity, and BED (e.g., Uher et al, 2005; Van den Eynde, 2010; Lowe et al, 2014; Kim et al, 2019; Alvarado-Reynoso, 2019).

In the therapeutic case series, participants will receive 20 sessions of iTBS. This decision is informed by rTMS and iTBS protocols from previous work in psychiatry, and from rTMS studies conducted by our own research group involving patients with anorexia nervosa. Historically rTMS and iTBS treatment protocols have employed anywhere between 5 and 35 treatment sessions, with studies citing psychiatric disorder, illness severity, and response to treatment as reason for the variation (e.g., Dunlop et al, 2015 used 20-30 sessions). 20 sessions of iTBS was chosen as this corresponds with our research groups previous work, is

equivalent to prevalent protocols used for the treatment of depression and mirrors the iTBS protocol used by Blumberger et al. (2018) in their large clinical trial assessing the effect of iTBS in depression.

6. Trial Objectives and Design

6.1 Trial Objectives

Overarching Aim

The overarching aim of this trial is to establish the feasibility and acceptability of iTBS in the patient population with refractory BED, and to assess the short- and long-term therapeutic effects of iTBS treatment. Two related studies will be conducted to address this aim: (1) a randomised, sham-controlled trial involving the delivery of a single session of iTBS and (2) a case series involving the delivery of 20 sessions of real iTBS over a four-week period.

1. In line with established recommendations for outcomes of feasibility trials [49], the primary aim is to assess the feasibility of using iTBS in this patient population and to acquire key information needed for the development of a large-scale randomised sham-controlled trial (RCT).

   The specific objectives of the proposed feasibility study are to:
   a. Establish the feasibility of conducting a large-scale RCT iTBS in patients with BED by assessing recruitment, attendance, and retention rates
   b. Determine the best instruments for measuring outcomes in a full trial by examining the quality, completeness, and variability in the data
   c. Estimate the treatment effect sizes and standard deviations for outcome measures to inform the sample size calculation for a large-scale RCT
   d. Evaluate whether the treatment is operating as it is designed by analysing process measures, such as within-session visual analogue scales of mood and hunger ratings
   e. Determine whether patients with BED evaluate iTBS as acceptable and credible
   f. Obtain information about patients' willingness to undergo random allocation to either real or sham iTBS administration

2. The secondary aim is to investigate the potential efficacy of iTBS for the treatment of BED. This will involve evaluating if:
   a. Real iTBS, as opposed to sham, is associated with short- and long-term improvement in clinical presentation; reduced frequency of objective binge-eating episodes, reduced food craving, reduced food intake, and improvement in other clinical outcomes in BED such as mood or physical health (i.e., BMI and adiposity).
   b. Real iTBS, as opposed to sham, has an effect on disorder-relevant neurocognitive parameters (e.g., impulsivity, inhibitory control, and reward-related decision making).

Primary endpoints

The central aim of this trial is to examine whether iTBS is a feasible treatment for patients with binge eating disorder. This will involve assessing recruitment, attendance and retention rates, and acceptability of treatment by participants. Acceptability and tolerability of the intervention will be informally assessed throughout the treatment (i.e., within-session) and following treatment completion using ad-lib patient feedback. Acceptability and tolerability will be formally assessed by asking all participants to indicate whether, following iTBS completion, they "would you consider iTBS treatment for yourself or for a friend?". Further, participants in the case series will be invited to complete an optional semi-structured interview relating to their treatment experience. Finally, drop-out rates will be assessed.

Secondary endpoints

The secondary endpoint involves establishing if iTBS was associated with improvement in core symptoms of BED and physical health at post-treatment and 3-month follow-up. Specifically, from pre-assessment, through to post-assessment and follow-up, patients with BED who received real iTBS are expected to report a greater reduction in a) the number of subjective and objective binge eating episodes, b) urge to binge, c) food-related craving, c) negative affect, d) and, in the case series only, improved indices of physical health (i.e., body mass index, body fat percentage and waist circumference). Secondary endpoints will be assessed using visual analogues scales (VAS), the food craving questionnaire (state version) [50], and a bogus taste test measure of food consumption in both the single-session RCT and the case series. In addition, clinically significant symptom change will be assessed in the case series using the Eating Disorders Examinations Questionnaire (EDE-Q; [51]), the Food Craving Questionnaire (Trait Version; [50]), the Depression, Anxiety

and Stress Scale (DASS-21; [52]), the Clinical Impairment Assessment (CIA; [53]), and anthropometric assessment.

An additional secondary endpoint involves investigating whether iTBS is associated with changes in the neurocognition at post-treatment and 3-month follow-up. In the RCT, change in delay-discounting will be assessed using a task proposed by Odum, Baumann and Rimington that assesses delay-discounting for both monetary and food rewards [54]. It is hypothesised that participants will demonstrate greater ability to delay gratification for both money and food following real, as opposed to sham, iTBS. Similarly, change in emotion regulation will be assessed using the emotion regulation task developed by Lang, Bradley and Cuthburt [55]. It is hypothesised that following real, as opposed to sham, iTBS participants will demonstrate improved emotion regulation as indicated by increased heart rate variability during the task. In the case series, change in neurocognitive performance from baseline to post-treatment and follow-up will be assessed for delay-discounting and emotion regulation, as well as for food-related decision making (using the food-choice task by Steinglass et al. [56]), and for inhibitory control (using the Go/No Go task by Fillmore et al. [57]). It is expected that following iTBS participants will display improved food related decision making, as indicated by reduced preference for high-fat, high-calorie foods, and improved performance on the Go/No Go task.

6.2 Trial Design

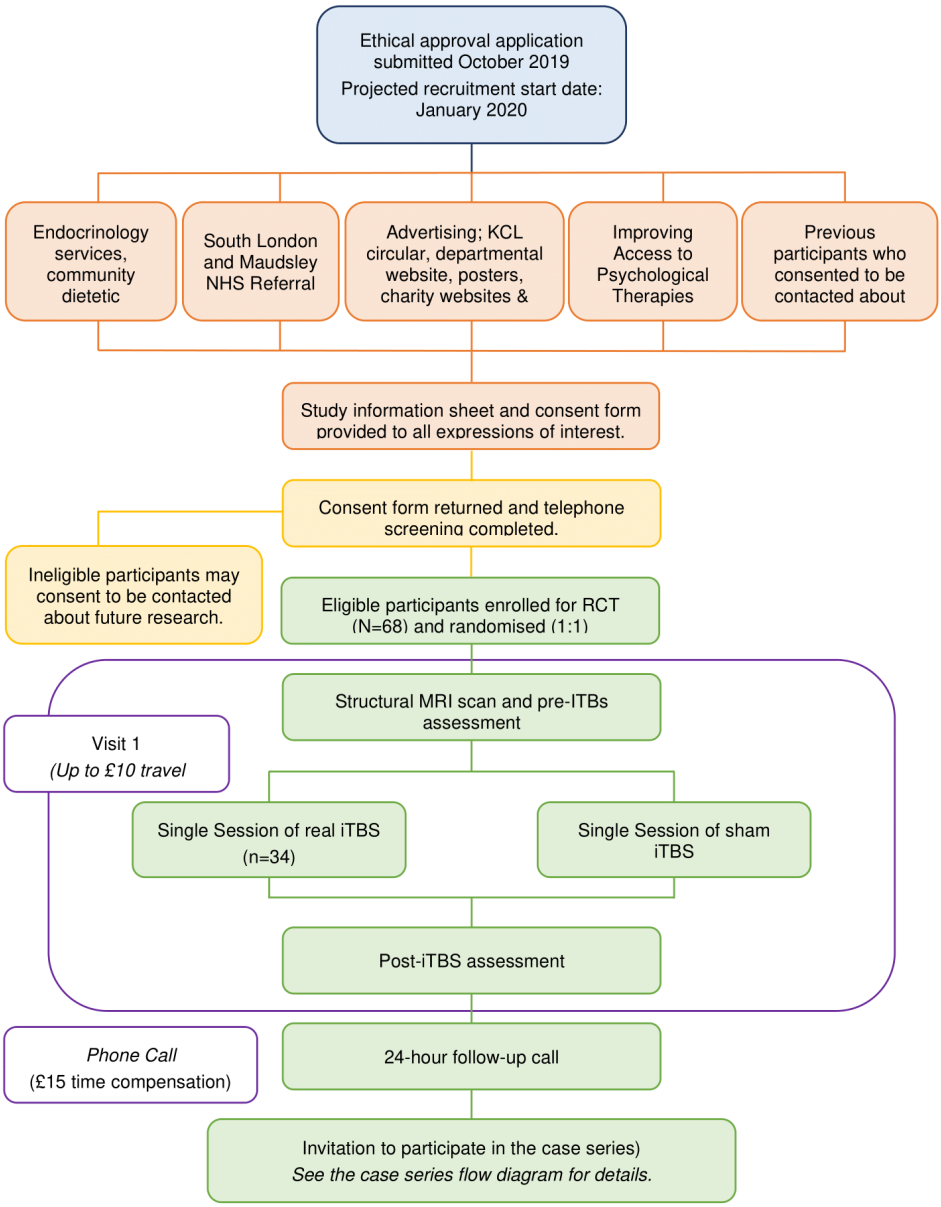
Two integrated, inter-related studies will be carried out: (1) a proof-of-concept randomised double-blind sham-controlled trial involving a single-session of either real or sham iTBS, and (2) a therapeutic case series involving 20 sessions of real iTBS delivered week-daily over four consecutive weeks. Participants will first take part in the proof of concept single session study then be invited to take part in the 20 session case series. All participants must take part in the single session study before taking part in the optional 20 session case series.

The RCT will involve a structural MRI scan (for the purposes of neuro-navigated iTBS) and the delivery of a single session of either real or sham iTBS. To control for satiety, participants will be advised to 3 hours prior to the participation session and asked to refrain from food consumption between this meal and their session. Both the participant and researcher will be blind to treatment allocation. Study measures will be completed at baseline, pre-iTBS, post-iTBS, and at over-the-phone 24-hour follow-up. Participants will attend one in-person study visits to complete baseline measures, receive iTBS and complete post-iTBS measures. Follow-up will be completed over the phone 24 hours post-iTBS. Study measures will include standardised questionnaires, visual analogue scales (VAS) relating to core BED psychopathology, a delay-discounting task [54] and an emotion regulation task . At follow-up, in addition to core questionnaire/VAS measures, participants will also be asked about adverse side-effects, the extent to which they consider iTBS an acceptable and tolerable treatment (e.g., “Would you consider iTBS as a potential treatment for yourself or for a friend?”) and about allocation/blinding (“Do you think that the iTBS treatment you received was real or sham?”). At the end of the RCT, blinding will be revealed, and participants will be invited to partake in the case series.

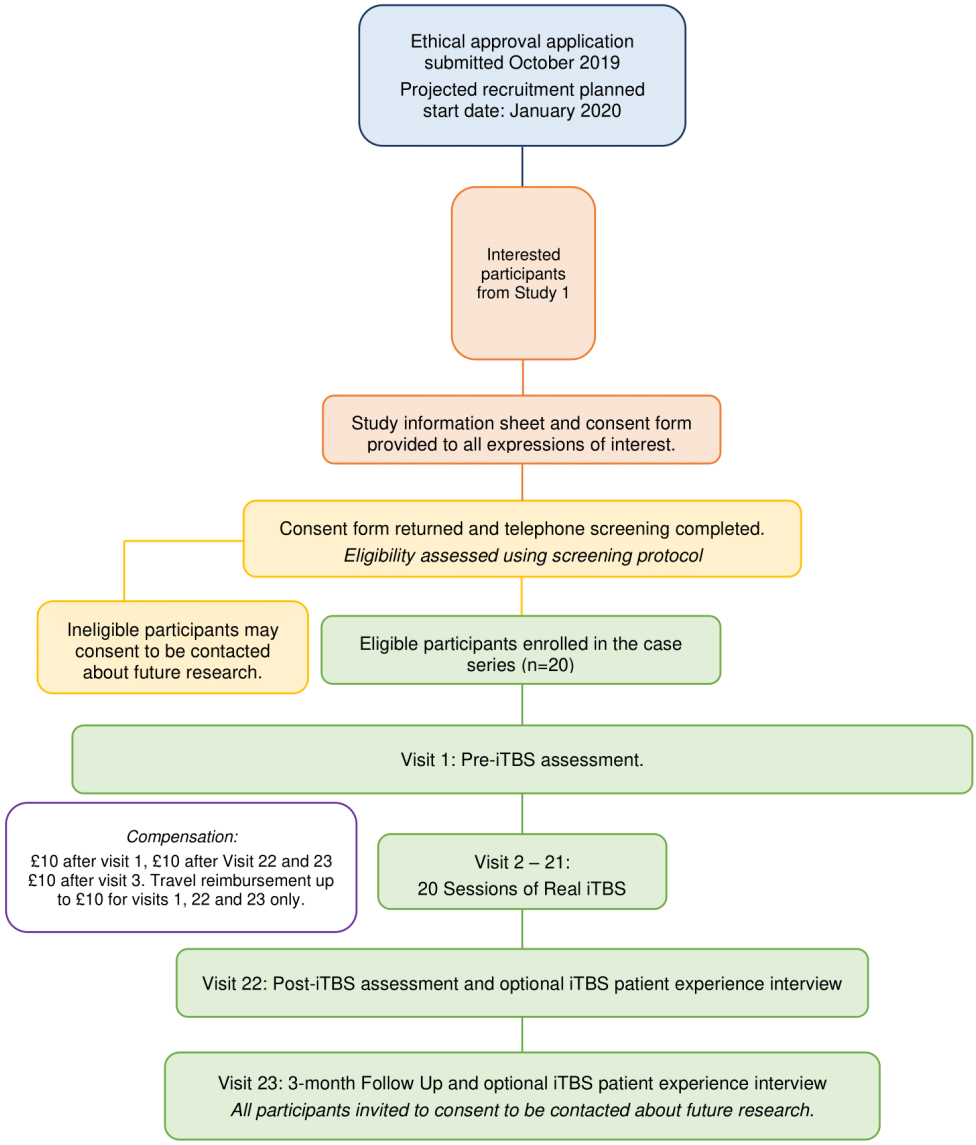
In the case series, all participants will receive active (real) iTBS. To control for satiety, participants will be asked to eat 3 hours prior to each session and asked to refrain from food consumption between this meal and their session. Case series participants will complete study visits at baseline, pre-treatment, post treatment and 3-months following the end of treatment (3-month follow-up). Study measures collected at baseline, pre-treatment, post-treatment and 3-month follow-up include VAS measures of core BED symptoms, standardised questionnaire measures (EDE-Q, DASS-21, Food Craving Questionnaire, and CIA), anthropometric measures of physical health, and neuropsychological tasks. Participants will also be invited to complete a semi-structured interview relating to their treatment experience at post-treatment and follow-up. During the treatment period, participants will complete a brief sub-set of core measures; at each session, episodes of binge eating from the previous 24 hours will be recorded and VAS measures will be completed. Each week, standardised psychological measures (EDE-Q and DASS-21) will be completed and anthropometrics data will be collected. Adverse side-effects will also be recorded at every session. The treatment protocol will involve 20 sessions of iTBS occurring week-daily over a 4-week period.

6.3 Trial Flowchart

Schematic diagram of the single-session RCT.



Schematic diagram of the 20-session case series.



7. Trial Intervention

7.1 Therapy/Intervention Details

Participants in this trial will receive intermittent theta bust stimulation (iTBS), a novel variant repetitive transcranial magnetic stimulation (rTMS). In TMS, an electrical current is passed through a TMS coil placed on the scalp. This generates a magnetic field, which is then pulsed in pre-defined patterns over a target region on the scull, altering cortical excitability in the structures immediately below. TMS may up- or down-regulate cortical excitability by using pulses that vary in length, form, intensity and pattern. Repetitive TMS involves the delivery of multiple magnetic pulses over a specified time-period and produces changes in cortical excitability that outlast the stimulation period (30-60 minutes) and may lead to lasting changes in brain function. High frequency rTMS (typically 10Hz) has been demonstrated to produce excitatory cortical effects. iTBS is a novel variant of excitatory rTMS which uses patterned-stimulation (triplet-bursts) to induce neuroplasticity. iTBS has been demonstrated to have a safety profile comparable to that of rTMS in both adolescents [58] and adults [30], and is proposed to produce equivalent therapeutic effects (See section 1 for further detail).

Participants in the RCT will receive a single session of either real or sham iTBS. Participants in the therapeutic case series will receive 20 sessions of real iTBS over 4 weeks (1 session every weekday for 4 consecutive weeks). In both studies, the following intervention details apply:

Localisation of the left DLPFC

All participants will undergo a structural magnetic resonance imaging (MRI) scan to enable localisation of the left DLPFC (using Brainsight™ neuro-navigation software). The protocol includes a high-resolution sagittal 3D T1-weighted volume (voxel size 1.1 x 1.1 x 1.2 mm^3) based on the well-validated ADNI protocol (http://adni.loni.usc.edu/methods/documents/mri-protocols/).

Determining the intensity of iTBS stimulation

The intensity of the iTBS will be determined by obtaining the participants resting motor threshold (rMT). Consistent with previous TBS studies in mental disorders (see Schwippel et al., 2019; [55] for review) stimulation will be delivered at 80% of rMT. Resting motor threshold (rMT) is defined as the stimulator intensity required to elicit at least five motor-evoked potentials (MEPs) with a 50-μV peak-to-peak amplitude out of ten consecutive stimulations when the coil is placed over the left primary cortex. In the RCT, rMT will be assessed once only. In the therapeutic case series, rMT will be assessed weekly to ensure the safety and efficacy of the intervention.

iTBS session(s)

A Magstim Rapid^2 Plus^1 device (Magstim®, UK) and Magstim D70-mm air-cooled real/sham coil will be used to administer real or sham stimulation. iTBS will be delivered at 80% of rMT intensity using standard stimulation parameters [27]; triplet-bursts will be delivered at high frequency (50 Hz) with an inter-burst interval of 200 ms. Each TBS train will last 2 seconds and consists of 10 triplet-bursts (30 pulses). Each iTBS session will involve 10 TBS trains repeated every 10 seconds for 190 seconds, with a total number of 600 pulses delivered during the session. Sham stimulation will be delivered using the same parameters as real iTBS however, a sham coil will be used. The sham coil makes the same noise and creates a similar sensation on the scalp as the real coil but does not produce a magnetic field. In the single session RCT participants will receive a total of 600 pulses of TBS. In the therapeutic case series, participants will receive a total of 12,000 TBS pulses over the course of treatment.

Intervention Risk:

This study uses a standard TBS protocol [27] which has been demonstrated to be safe for use in both adults [30] and adolescents [58]. The stimulation parameters used parameters have been used in many other studies with varying adult and adolescent populations, including those with neurological disorders, neurodevelopmental disorders and psychiatric disorders.

The most commonly reported side effect of rTMS is transient headache and neck pain; Oberman, Edwards, Eldaif and Pascual-Leone's systematic review reports that only 3% of participants receiving TBS report this adverse event [30]. At each stimulation session (one session for the RCT and 20 sessions for the case-series) TBS related discomfort and adverse events since the previous session will be assessed. Both the real and sham coil produce a loud noise during stimulation; Though the noise is not loud enough to damage hearing, participants will be asked to wear earplugs to minimise discomfort. The coil may also become hot during stimulation however, the temperature will only rise slightly above body-temperature and damage to

skin or hair have not been reported previously. An inbuild mechanism also ensures that the coil is automatically switched off if the temperature reaches 40 degrees Celsius. Finally, although TMS and TBS are considered safe, the most serious side effect is seizure, although this is very rare; Oberman et al. reported that a seizure has only occurred once with TBS to date and proposes a crude risk of seizure per session of 0.02%[30].

7.2 Frequency and duration of intervention

The RCT involves the delivery of one session of iTBS. The duration of this session is approximately 90 minutes; 15 minutes for preparation of the iTBS equipment (i.e. calibrating the neuro-navigation system, locating the dorsolateral prefrontal cortex, and assessing rMT) and approximately 3 minutes of iTBS stimulation.

The case series will involve the delivery 20 sessions of real iTBS delivered week-daily over a 4-week period. This program for stimulation is equivalent to the treatment protocol used in depression. In the therapeutic case series, each treatment session will last approximately 30 minutes in total; 10-15 minutes for preparation of the study equipment (i.e. calibrating the neuro-navigation system, locating the dorsolateral prefrontal cortex, and assessing rMT), approximately 3 minutes of iTBS stimulation, and 10 minutes for the completion of core study measures. Resting MT will be assessed weekly to ensure the safety and efficacy of intervention.

7.3 Subject Compliance

A researcher will be present for all TBS and assessment sessions to ensure participant attendance and task compliance.

7.4 Study adherence

A researcher will be present for all TBS and assessment sessions to ensure study adherence. Any deviation from the study protocol will be recognised and recorded immediately.

7.5 Concomitant Medication

Psychotropic medication other than antidepressant medication is an exclusion criterion at intake (patients have to be on stable medication of an antidepressant for at least 14 days prior to participation in the trial). Participants will have completed a consent form that outlines their responsibility to inform the study researcher of any changes to their medication or of any new medical diagnoses made during their participation in the study. Participants enrolled in the trial who report such a change will be evaluated on a case-by-case basis by the study researcher and co-investigators (PhD supervisors), and a consensus may result in the termination of a participant's involvement in the study as a precautionary safety measure.

8. Research Environment

All study data relating to treatment sessions, measures and tasks will be collected at the IoPPN campus in King's College London, and questionnaire and scale data will be collected via online survey software or hardcopy questionnaires.

9. Selection and Withdrawal of Subjects

9.1 Inclusion Criteria

- Male and female community-dwelling adults between 13 and 60 years of age, who are overweight or obese according to WHO criteria (BMI>25 kg/m²)
- Meet criteria for full-syndrome DSM-5 Binge Eating Disorder (BED)
- Right-handed
- Must use and understand English as a language for everyday conversation
- Must receive approval to participate from their general practitioner and, where relevant, their eating disorder therapist

9.2 Exclusion Criteria

- All known contraindications to MRI and TBS (assessed using TMS and MRI safety screening questionnaires)
- Pregnancy (queried at screening and confirmed by pregnancy test prior to starting participation)
- History of neurological disease and/or seizure

- Having any metallic implants anywhere in the head or body
- History of head or eye injury
- Significant health problems in the previous six months
- Lifetime diagnosis of substance dependence, psychosis, bipolar disorder, borderline personality disorder
- Other primary psychiatric disorder requiring treatment in its own right
- Taking psychotropic medication other than a stable dosage of selective serotonin reuptake inhibitors (SSRI) for at least 14 days prior to study enrollment
- Adults consuming more than 14 units of alcohol per week who are unwilling to reduce their alcohol intake for the duration of the treatment. Participants under 18 years who report alcohol consumption will be required to abstain from alcohol consumption for the duration of the study.
- Cigarette consumption or nicotine replacement exceeding >15 cigarettes daily or equivalent. Participants under 18 years who report cigarette (or nicotine replacement) use will be required to abstain from nicotine use for the duration of the study.
- Current illicit drug use.

9.3 Selection of Participants

Participants will be recruited via different routes:

1. Potentially suitable patients from Adult and Child & Adolescent Eating Disorders Outpatient services at the South London and Maudsley NHS Foundation Trust (SLaM) will be approached by the clinical team.
2. Public facing study advertisements will be distributed across KCL via the KCL circular mail and via posters placed on noticeboards at various KCL locations. Social media platforms such as the KCL Eating Disorders Unit official Twitter account will also be used to advertise the study. Individuals who have previously taken part in research studies in the KCL Eating Disorders Unit that consented to be contacted about future research will also be contacted by email or phone.
3. The study will be advertised by Beat (UK's leading eating disorder charity). Study information will be placed on the charity's website and social media platforms. Similarly, websites such as www.callforparticipants.com and www.mqmentalhealth.org may also be used.
4. Study advertising materials (e.g., leaflets or posters) will be available from endocrinology services and community dietetics services in South London.

Participants from the single-session RCT will all be invited to take part in the case series.

9.4 Randomisation Procedure / Code Break

The single-session study will be a randomised, double-blind, sham-controlled trial. Participants will be randomly allocated to a treatment condition (real or sham) in a 1:1 ratio. To ensure researcher blinding, the randomisation sequence will be generated and managed by an independent researcher within the Section for Eating Disorders. This researcher will reveal treatment allocation to participants in the RCT at the end of their participation.

9.5 Withdrawal of Subjects

Participants have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw a participant from the study in the event of inter-current illness, protocol violation, or for administrative or other reasons. It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible.

9.6 Expected Duration of Trial

Time from first patient first visit to last patient last visit (including follow-up) is expected to be 21 months.

10. Trial Procedures

10.1 Procedures by Visit

Recruitment and participant information

Interested participants will contact the researcher directly or, if requested, they will be contacted by the researcher (e.g., participants recruited from specialist ED services may ask their clinical team to arrange for the researcher to contact them directly). All who enquire about the study (and where appropriate their parent/carer) will be sent an information sheet and 3 copies of the consent form (via email or post) to be reviewed. All will be encouraged to read through these documents and to contact the researcher if they require further information. Any participant, parent or carer requiring further information will be invited to attend an information session during which the study background, hypotheses, and protocol will be explained. This session will not be time-limited and all questions from the patient will be answered. All potential participants, parents or carers will be given the option to receive an equivalent detailed description of the study over the phone if they prefer.

Interested participants will be required to return 3 copies of the signed consent form to the researcher prior to screening. Where the participant is under 16 years of age, a parent/carer will be required to sign the consent forms, and the young person will be required to sign to indicate their assent. The researcher will sign the returned consent forms and return one copy to the participant, keep one for their own records, and provide one to the participant's GP after eligibility is confirmed at screening. Once all consent forms have been completed, a 20-minute screening call will be scheduled.

Screening

All participants will be screened by phone or in person, depending on their preference. Screening measures will be completed as follows:

1. Eating Disorder Diagnostic Screen (EDDS) [60]: The EDDS is a questionnaire that assesses symptoms of eating disorders. It will be administered at the beginning of the screening to confirm a BED diagnosis.

2. MRI Safety Screen: The King's College London Centre for Neuroimaging Science MRI safety screen for contraindications to MRI.

3. TMS Adult Safety Screening Questionnaire [61]: The TMS adult safety screening questionnaire will be used to check for contraindications to TMS in all participants. While some participants will be in the adolescent age range, comprehensive reviews of safety and ethical guidelines for TMS by Rossi et al. [46] and Krishnan et al. [62] indicate that there are no additional safety considerations for the delivery of TMS to adolescents and young adults.

4. General Health and Lifestyle Questions: At screening potential participants will be asked about their general health to ensure they are suitable for iTBS. Questions ask about regular medications, history of serious physical and mental health problems, allergies, cigarette use, and alcohol consumption.

A copy of the full screening interview is included with this submission.

After screening, if eligibility is confirmed, the participant will be formally enrolled into the study, and invited to take part in the single session RCT. When the participant is formally enrolled in the study, they will be assigned a unique identifier which will be used to label all data provided by that participant for the duration of the study.

Participants will also be invited to attend an optional mock MRI scan to familiarise them with the MRI environment and minimise anxiety during the study scanning session.

Those deemed ineligible at screening will be thanked for their time and invited to consider whether they would like to be contacted about future related studies.

After completing the single session RCT they will be invited to decide whether they wish to take part in the 20-session case series. Where participants choose to participate in both the single-session RCT and the therapeutic case series, participants will be required to repeat screening prior to commencing the case series to ensure continued eligibility.

Single-Session Randomised Control Trial – Procedures by Visit

Participants will be randomly allocated to a treatment condition (real or sham) in a 1:1 ratio. Full participation in the RCT will take approximately 3.5 hours and will take place at King's College London, IoPPN (visit 1) and over-the-phone (follow-up).

Visit 1

Participants will be asked to fast for 3 hours prior to Visit 1. On arrival, all participants will complete a 15-minute structural MRI scan for the purposes of neuronavigated iTBS. Prior to the MRI, biological female participants will be asked to take a pregnancy test to ensure they do not need to be excluded for safety reasons. The structural MRI scan will take place at the Centre for Neuroimaging Sciences (CNS) and will last 15 minutes. Scans will be completed by a qualified neuroradiologist and participants will complete the CNS MRI consent form with the neuroradiologist prior to the scan. This form includes questions about MRI safety, all have which will have previously been completed with the participant at screening. It is routine procedure to complete these questions prior to providing consent to scan on the day.

Following the scan, the participant will be invited to take a short break and asked to refrain from eating during this time. During the break the researcher will prepare the lab for the iTBS session (i.e., upload the participants MRI scan to Brainsight®).

When the session recommences, ED symptoms and general psychopathology will be collected using the following measures. All participants will complete tasks in the same order and will have a break of 2-3 minutes between tasks/measures to minimise fatigue:

1. Eating Disorder Examination (EDE-Q) [63]: The EDE-Q is a widely used measure of eating-disordered behaviour and is regarded as the instrument of choice for the assessment of clinical eating disorders. The EDE-Q has been used extensively in both adult and adolescent samples and researchers have developed community norms and an amended scoring structure for use in adolescent research [64].

2. Depression, Anxiety and Stress Scale (21-item version; DASS-21) [52]: This is a 21 item self-report questionnaire which aims to evaluate mood, anxiety and stress levels over the previous week. The DASS-21 is a widely used assessment of negative affect that has been demonstrated to have strong psychometric properties in both adults [52, 65, 66] and adolescents [67].

3. Food Cravings Questionnaire (Trait Version; [50]): This is a 15 item, self-report questionnaire that measures trait levels of craving for food across 9 domains; anticipation of positive reinforcement from eating, anticipation of relief from negative affect after eating, having intentions or plans to consume food, cues that may trigger cravings, thoughts or preoccupation with food, craving as hunger, lack of control around food, emotions that may be experienced before, during and after craving, and guilt relating to craving. The Food Craving Questionnaires (State and Trait Versions) are widely used and strong psychometric properties have been reported in adult samples. Wider application of this measure to adolescent research has been encouraged [68].

4. Emotion Regulation Questionnaire (ERQ) [69]: A 10-item scale designed to measure respondents' tendency to regulate their emotions in two ways: (1) cognitive reappraisal and (2) expressive suppression. Respondents answer each item on a 7-point Likert-type scale ranging from 1 (strongly disagree) to 7 (strongly agree). The ERQ was developed and validated for use in adult populations. An adaptation of the measure has been developed and validated for use in children and adolescents(ERQ-CA; [70]). As such, adolescent participants (aged 13-17) will complete the ERQ-CA.

5. Demographic information relating gender, marital status, living situation and education will be collected.

6. Body Composition and physical health measures will be taken. The researcher will measure the participants' height in centimetres (cms) and weight in kilograms (kgs) and use bioelectrical impedance

analysis (BIA) to assess body fat percentage and waist circumference. BIA is a commonly used non-invasive procedure in which a weak electric current flows through the body and the voltage is measured to calculate impedance (resistance) of the body.

Participants will be asked to report episodes of binge eating from the previous 24 hours. Visual analogue scales (VAS; 10cm) assessing current hunger, craving for food, feeling of fullness, urge to eat, urge to binge eat, feeling low, level of tension, level of stress and level of anxiety will then be completed (T0 VAS).

Once these measures have been completed, participants will perform a computerised delay-discounting task involving items about both food and money ([34], DD*pre)*. The delay discounting task, developed by Odum, Baumann, & Rimington, 2006, examines whether small amounts of food would be discounted more steeply than money, as occurs with larger amounts. Participants indicate their preferences in a series of choices for two hypothetical outcome types: immediate versus delayed food and immediate versus delayed money. Participants make choices involving either relatively small maximum amounts of food (£10 worth) and money (£10) or for relatively large maximum amounts of food (£100 worth) and money (£100). Performance on this task can be used to study self-regulation, delayed gratification and valuation of reward. The delay discounting task takes approximately 20 minutes to administer. Delay discounting paradigms have been used extensively in both adult and adolescent populations with and without ED [71, 72].

Following this, participants will complete an emotion regulation task (ER*pre)*. The emotion regulation task measures participants heart rate during the presentation of 40 highly aversive and arousing pictures from the International Affective Picture System curated by Lang, Bradley & Cuthbert (1997, [55]). Heart rate will be measured as a reflection of autonomic nervous system functioning and as an index of emotion regulation.

Participants will then complete the food challenge task (FCT*pre*). The food challenge task will be used to examine cue-induced food craving. In this task, participants rate their state food craving using the Food Cravings Questionnaire (State Version; [14]) after being presented with a video of highly palatable foods (Marks and Spencer's adverts) on a computer screen. The food challenge task has been used previously by our research group in studies involving adult participants [26, 35, 36]. This task has not been used in an adolescent sample previously, though it is expected that the stimuli and measures used will be age appropriate. After completing the food challenge task, VAS measures will be repeated (T1 VAS).

Resting motor threshold (rMT) will then be measured and real/sham iTBS will be delivered as per the intervention protocol. Following stimulation, a 10cm VAS measuring discomfort experienced during the iTBS will be completed. The food challenge task (FCT*post)*, VAS measures (T2 VAS), delay discounting task (DD*post)*, and emotion regulation (ER*post)* tasks will then be re-administered.

Finally, participants will complete the bogas taste test task. Actual food consumption will be measured using a bogus "taste test." Participants are instructed to rate 3 bowls of palatable high-calorie food items (chocolate, biscuits, crisps) in terms of their visual, attractiveness, smell, and taste. They are given 10 minutes to complete their ratings and will be told that they are free to eat as much of the offered items as they like. Consumption will be determined by weighing the bowls before and after the "taste test" and the difference in weight from pre-to post-assessment will be converted into calories and used as a measure of food intake. VAS measures will be repeated at the end of the study visit (T3 VAS).

Follow-Up

At 24-hours post-iTBS, participants will be contacted by phone for follow up. This call will last approximately 20 minutes. During this call, participants will report adverse events that may be related to the iTBS treatment (e.g., headache or neck pain), report episodes of binge eating in the 24-hour period since the iTBS session, and complete VAS measures (T4). They will also be asked a) "Do you think that the theta burst stimulation you received was real or sham?" and b) "If iTBS was found to be efficacious in BED, would you consider this treatment for yourself, or recommend it to a friend?" Following this blinding will be revealed and participants will be invited to participate in the case series.

RCT procedures by visit are illustrated in Figure 1 below.

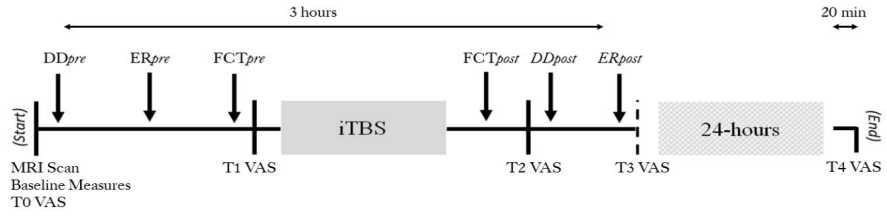


Figure legend: VAS=visual analogue scales, DD=delay discounting task, ER=emotion regulation task, FCT=food challenge task

Case Series - Procedures by Visit

Where participants choose to complete both the single-session RCT and the therapeutic case series, participants will be required to repeat screening prior to commencing the case series to ensure continued eligibility.

Pre-treatment assessment (Visit 1)

The pre-treatment assessment will take place no more than 3 days prior to commencing iTBS (e.g., participants may complete the baseline assessment on a Friday before commencing treatment on a Monday, or alternatively complete the baseline assessment one weekday prior to commencing iTBS). Visit 1 will take place at King's College London IoPPN and last 2 hours.

During this visit participants will complete a range of questionnaire measures and computer-based tasks. All participants will complete tasks in the same order and will have a break of 2-3 minutes between tasks/measures and be offered a longer 15-20-minute break after 1 hour, to minimise fatigue. As in the single-session RCT, participants will have their height, weight and body composition measures taken, and complete the Eating Disorder Examination (EDE-Q) [63], the Depression, Anxiety and Stress Scale (21-item version; DASS-21) [52], Food Cravings Questionnaire (Trait Version; [50]), the emotion regulation questionnaire (ERQ [67]), visual analogue scales (VAS), the food challenge task (FCT), the delay discounting task (DD) [54], the emotion regulation task (ER) [55] and the bogas taste test. In addition, participants will also complete:

1. Clinical Impairment Assessment (CIA) [73]: The CIA is designed to assess quality of life by exploring the perceived effects of having an ED on various domains, including social, emotional and cognitive aspects. It is a 16-item self-report measure of the severity of psychosocial impairment due to eating disorder features and focuses on the past 28 days. The 16 items cover impairment in domains of life that are typically affected by eating disorder psychopathology: mood and self-perception, cognitive functioning, interpersonal functioning and work performance. The purpose of the CIA is to provide a simple single index of the severity of psychosocial impairment secondary to eating disorder features. The CIA has been used in previous research using both adult and adolescent samples. Psychometric studies of the CIA have shown satisfactory reliability and validity in adult samples, with one study reporting support for its use in adolescents [74-77].

2. Barrett Impulsiveness Scale (BIS-11) [78]: This questionnaire is designed to assess the personality/ behavioural construct of impulsiveness. The current version is composed of 30 items describing common impulsive or non-impulsive behaviours and preferences. It is the most widely cited instrument for the assessment of impulsiveness. The BIS-II has been found to have sound psychometric properties in both adult and adolescent populations, and normative data is widely available [79]. In adolescents studies, some authors have used modified items to be more appropriate for the adolescent life stage experiences and to avoid content bias (e.g., item 16 was reworded to "I change my mind about what I will do when I grow up" from "I change jobs"; item 21 was reworded to "I change friends" from "I change residences" [80, 81]). However, review by Vasconcelos and colleagues (2012) suggests that these modifications did not influence the construct representation. As such, these modifications will also be made for adolescent participants in the present study.

3. Delayed Gratification Inventory (DGI) [82]: This questionnaire assesses participants' ability/tendencies to delay gratification for five domains (food, physical pleasures, social interactions, money, and achievement). Participants are asked to reflect on their experiences and rate how strongly they agree/disagree with the given statements. The DGI was developed and validated in a large adult sample and sound psychometric properties are reported [82]. This measure has not previously been used in adolescent research and, given that several domains may not be relatable/appropriate for younger participants, this measure will not be completed by adolescents (participants under 18).

4. The 21-item Power of Food Scale (PFS) (Lowe, 2009): This scale assesses the psychological influence of the mere presence or availability of food. It measures appetite for, rather than consumption of, palatable foods, at three levels of food proximity (food available, food present, and food tasted). The Power of Food scale has strong psychometric properties in obese and community adult populations

[83], and is considered appropriate for us above the age of 13 years. Up to age 13, the Children's Power of Food Scale is recommended [84]. Given participants will be aged between 13 and 70 years, all will complete the adult version of the scale.

5. The Yale Food Addiction Scale Version 2.0 (YFAS 2.0; Gerhardt, Corbin, & Brownell, 2016). The YFAS 2.0 reflects the current diagnostic understanding of addiction to further investigate the potential role of an addictive process in problematic eating behaviour. The 35-item scale includes items that assess specific criteria, such as diminished control over consumption, a persistent desire or repeated unsuccessful attempts to quit, withdrawal, and clinically significant impairment. The YFAS has received psychometric support in clinical populations [85] and has been used in adults and adolescents [86].

6. Positive and Negative Affect Schedule (PANAS) [87]: The PANAS consists of two 10-item self-report scale which measures 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. The PANAS is one of the most widely used measures of affect, and has been validated for use in both adults [88] and adolescents [89].

7. Go/No-Go task (Fillmore, 2003): The cued go/no go task is a useful measure of impulse control in clinical populations. This task is a classic test of executive function, requiring effortful response inhibition. The cued go no-go task measures impulse control by the ability to inhibit instigated, prepotent responses. The task manipulates response prepotency by presenting a preliminary go or no-go cue before the actual go or no-go target is displayed. The cues provide information concerning the probability that a go or no-go target will be presented. The cue-target relationship is manipulated so that the cues have a high probability of correctly signaling a go or no-go target (valid cues), and a low probability of incorrectly signaling a target (invalid cues). Valid cues tend to facilitate response inhibition and speed response execution, whereas invalid cue cues tend to impair response inhibition and slow response execution. The Go/No-Go task takes 15 minutes to complete. Go/No Go paradigms are well established measures of response inhibition which have been used extensively across adult and adolescent studies, including populations with ED [90, 91].

8. Food choice task [56]: This task assesses decision making regarding food selection. Participants rate 43 food images (including high-fat and low-fat items) for healthiness and tastiness; an item rated neutral on both blocks was then selected as the reference item. On each of 42 subsequent trials participants choose between the food item presented and the reference item. The food choice task takes approximately 20 minutes to complete. The food choice task is a relatively new task which has not previously been used in adolescents. It is expected that the task will be appropriate for administration in this population, and that responses will be informative for future research.

iTBS Visits (Visit 2 – Visit 21):

20 sessions iTBS will be delivered week-daily at the IoPPN rTMS lab over the course of 4 weeks. See section 8 for a detailed description of the intervention procedure.

The following measures will be collected weekly:

1. Anthropometric measures.
2. Depression, Anxiety and Stress Scale (21-item version; DASS-21)
3. Food Cravings Questionnaire (Trait Version)

The following measures will be completed at every iTBS visit:

1. Adverse events will be reported (e.g., headache, neck pain).

2. Episodes of objective binge-eating from the previous 24 hours will be reported.

3. Participants will complete the food challenge task and VAS measures prior to and following iTBS.

4. VAS measure of iTBS discomfort (ranging from “none” to “extreme discomfort”) will be completed.

Post-Treatment (Visit 22):

The post-treatment assessment (visit 22) will be completed at King's College London IoPPN on the first weekday immediately following completion of iTBS treatment, at the same time of day as the pre-treatment assessment. The post treatment assessment will take approximately 2 hours. All tasks and measures from the pre-treatment assessment will be repeated, with 2-3 minutes between measures and tasks, and an optional 15-20-minute break halfway through the session, to minimise fatigue. In addition to the measures and tasks included in the pre-treatment assessment, participants will also be invited to complete a short, semi-structured interview about their experience receiving iTBS treatment, for the assessment of patient acceptability and treatment credibility. Where appropriate, parent(s)/carer(s) will also be invited to complete a semi-structured interview with the researcher about the iTBS treatment process, and to share their views about the acceptability and credibility of the treatment. Copies of these semi-structured interviews are included in this submission.

3-Month Follow Up (Visit 23):

3-months after the post treatment session (i.e., 4 months from the beginning of iTBS treatment) participants will attend a follow-up assessment at King's College London IoPPN. This session will take approximately 2 hours. Assessment procedures will be the same as for the post-treatment assessment.

At the end of their participation, all participants will be thanked for their time and invited to consent to be contacted about future related research.

10.2 Table summarising study measures and tasks by visit

Table 1. Summary of the frequency of questionnaires, scales and tasks for the proof-of-concept single-session RCT.

	Screening Call	Visit 1		Over-the-Phone Follow Up
		Pre-TBS	Post-TBS	
Eating Disorder Diagnosis Confirmation	X			
TMS & MRI Safety Screen	X			
General Health and Lifestyle Questionnaire	X			
Structural MRI Scan		X		
Physical Health Measures		X		
Demographics		X		
Eating Disorder Examination Questionnaire (EDE-Q)		X		
Depression, Anxiety, Stress Scale (DASS-21)		X		
Emotion Regulation Questionnaire (ERQ)		X		
Food Craving Questionnaire – Trait Version		X		
Delay Discounting Task		X	X	
Emotion Regulation Task		X	X	
Food Challenge Task		X	X	
VAS Measures of Core BED Psychopathology		X	X	X
Assessment of iTBS Side Effects/Discomfort			X	X
Taste Test			X	
Assessment of Acceptability				X
Blinding Assessment				X

Table 2. Summary of the frequency of questionnaires, scales and tasks for the 20-session case series.

	Screening	Pre-Assessment	During Treatment		Post-Assessment	3-Month Follow Up
			Weekly	Daily		
Eating Disorder Diagnosis Confirmation	X					
TMS Safety Screen	X					
General Health and Lifestyle Questionnaire	X					
Demographics		X				
Physical Health Measures		X			X	X
Eating Disorder Examination Questionnaire (EDE-Q)		X	X		X	X
Depression, Anxiety, Stress Scale (DASS-21)		X	X		X	X
Food Craving Questionnaire – Trait Version		X	X		X	X
Power of Food Scale (PFS)		X			X	X
Yale Food Addiction Scale YFAS)		X			X	X
Clinical Impairment Assessment (CIA)		X			X	X
Emotion Regulation Questionnaire (ERQ)		X			X	X
Positive and Negative Affect Schedule (PANAS)		X			X	X
Barrett Impulsiveness Scale (BIS-11)		X			X	X
Delayed Gratification Inventory (DGI)		X			X	X
Food Challenge Task		X		X	X	X
VAS Measures of Core BED Psychopathology		X		X	X	X
Delay Discounting Task		X			X	X
Emotion Regulation Task		X			X	X
Go/No Go Task		X			X	X
Food Choice Task		X			X	X
Bogus Taste Test		X			X	X
Assessment of iTBS Discomfort/Side Effects				X	X	X
Assessment of Acceptability					X	X

10.3 Laboratory Tests

No laboratory tests required.

11. Assessment of Efficacy

11.2 Primary Efficacy Parameters

The primary outcome of this proof-of-concept feasibility study is to establish the feasibility and acceptability of iTBS in the patient population with refractory BED, to assess the short- and long-term therapeutic effects of iTBS in this population, and to acquire key information to inform the development of a large-scale RCT. In line with recommendations by Eldridge et al., 2016, the primary outcomes for the proposed study are to:

a. Establish the feasibility of conducting a large-scale RCT iTBS in patients with BED by assessing recruitment, attendance, and retention rates
b. Determine the best instruments for measuring outcomes in a full trial by examining the quality, completeness, and variability in the data
c. Estimate the treatment effect sizes and standard deviations for outcome measures to inform the sample size calculation for a large-scale RCT
d. Evaluate whether the treatment is operating as it is designed by analysing process measures, such as within-session visual analogue scales of mood and hunger ratings
e. Determine whether patients with BED evaluate iTBS as acceptable and credible
f. Obtain information about patients' willingness to undergo random allocation to either real or sham iTBS administration

11.3 Secondary Efficacy Parameters

The secondary outcomes involve investigating if real iTBS has therapeutic benefits and assessing whether these are superior to sham iTBS. This involves examining:

a) Differences between pre-real/sham iTBS VAS scores and post real/sham iTBS VAS scores
b) Differences in pre-real/sham iTBS performance on tasks of delay discounting and emotion regulation and post real/sham iTBS delay discounting and emotion regulation.
c) Change in performance on task measures of delay discounting, emotion regulation, food-related decision making and inhibitory control from pre-iTBS to 3-month follow up.
d) Change in scores on the EDE-Q, specifically indicators of change in the frequency of objective binge eating episodes, and DASS-21, from pre-assessment to the 3-month follow-up.
e) Change in physical health; specifically body mass index, adiposity, waist circumference and cardiovascular health, from pre-iTBS to 3-month follow up.

11.4 Procedures for Assessing Efficacy Parameters

Procedures for assessing efficacy parameters involve the use of extensive questionnaires, measurement scales and tasks outlined under 11.

12. Assessment of Safety

All TBS study procedures and parameters are in accordance with current safety and application guidelines for rTMS. Treatment will be delivered by personnel trained in the administration of TBS. A case record form for each trial patient will be kept for monitoring session attendance and any side effects or adverse events. Any protocol violations will also be recorded here. In the event of mild side effects (such as headache) participants will not be withdrawn but will be able to discontinue TBS if they wish. TBS will be immediately halted if the participant experiences a more serious adverse event (such as an epileptic seizure) or if any other indicators of medical risk emerge. Treatment will only be restarted if it is deemed safe to continue by a medical professional. Throughout the study, participants will be able to access or continue treatment as usual (TAU) as recommended by their healthcare provider.

12.1 Specification, Timing and Recording of Safety Parameters

All TBS procedures and parameters are in accordance with current safety and application guidelines for rTMS.

12.2 Procedures for Recording and Reporting Adverse Events

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a therapy has been administered including occurrences which are not necessarily caused by or related to that therapy.

Adverse Reaction (AR): Any untoward and unintended response in a subject to a therapy which is related to any duration of therapy administered to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information known about the therapy in question in the view of the investigator.

Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

- Results in death;
- Is life-threatening;
- Required hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect;

Reporting Responsibilities

All SARs and USARs will be reported immediately by the Chief Investigator to the R&D office.

TBS can occasionally result in mild side-effects (including headache or neck pain). Participants have the option to withdraw from the study and terminate their participation if they experience discomfort during TBS. Similarly, they have the option to withdraw immediately if they wish to terminate their participation for any other reason that they may or may not wish to disclose. Participants who are at-risk for adverse side effects will be excluded from the study at the screening stage.

If a child under 16 discloses substance use when completing screening for this study, we will the UK General Medical Council Principals for Confidentiality when deliberating our responsibility to disclose. These guidelines state that when considering whether disclosure (to a legal guardian, healthcare professional or other relevant authority) would be justified you should:

a) tell the young person what you propose and why, providing doing so would not put the young person at increased risk of harm and,

b) where the young person has capacity to provide consent, ask for consent from to disclose is it is possible to do so.

The researchers will report any UARS, SARS and USARS.

Adverse events that do not require reporting: Patients with eating disorders are at an increased risk of self-harm. Incidents of self-harm may require medical attention.

12.3 Stopping Rules

The trial may be prematurely discontinued by the Sponsor or Chief Investigator on the basis of new safety information.

13. Statistics

13.1 Sample Size

As the proposed study is a feasibility study, an a priori sample calculation is not necessary. Rather, its aim is to provide effect sizes on which future large-scale studies can be powered. Total sample sizes of n=24 to n=50 have been recommended for feasibility trials with a primary outcome measured on a continuous scale, mainly because estimates of the standard deviation for normally distributed variables tend to stabilise around this size (Lancaster et al., 2004, Julious, 2005). We have chosen a target end sample size of n=60 for the single-session RCT and n=20 for the case series. Based on previous work in EDs (Schmidt et al., 2012, Schmidt et al., 2013), we expect an attrition to follow-up rate of a = 0.10 (as found in previous eating disorder trials. As such, to allow for balanced groups, we will recruit an actual sample size of 68 for the RCT and 22 for the case series.

13.2 Randomisation

Single Session RCT

Participants will be randomly allocated to a treatment condition (real or sham) in a 1:1 ratio. To ensure researcher blinding, the randomisation sequence will be generated and managed by an independent researcher within the Section for Eating Disorders. This researcher will reveal treatment allocation to participants in the RCT at the end of their participation.

Therapeutic case series

Participants will not be randomised; all will receive real iTBS treatment.

13.3 Analysis

Feasibility outcome data:

Feasibility outcome data will be analysed with appropriate summary statistics.

Clinical outcome data:

To determine quality, completeness, and variability of the outcome measures, descriptive statistical analyses and graphical methods will be used. For the RCT, the effects of real versus sham iTBS on core symptoms of BED (summation of scores on the VAS measures) over time will be evaluated using paired and independent t-tests (i.e., both between and within group comparisons). In the case series, the size of the treatment effect will be determined using the Jacobson-Truax method. This method is a change score approach in which intra-individual comparisons are conducted at pre- and post-treatment. Change scores will be calculated for eating disorder symptoms (EDE-Q), craving (Food Craving Questionnaire – Trait Version), and negative affect (DASS-21), as well as neurocognitive task performance.

14. Trial Steering Committee

This small-scale study does not have the resources in place to establish a trial steering committee.

15. Data Monitoring Committee

This small-scale study does not have the resources in place to establish a data monitoring committee. Data monitoring will be managed by the research team (Michaela Flynn, Professor Iain Campbell and Professor Ulrike Schmidt).

16. Direct Access to Source Data and Documents

The Investigator(s) will permit trial-related monitoring, audits and REC review by providing the Sponsor(s), and REC direct access to source data and other documents.

17. Ethics & Regulatory Approvals

This trial will be conducted in compliance with the study protocol, the Declaration of Helsinki, the principles of good clinical practice (ICH-E6 guideline), the ICH-E8 guideline, the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the UK policy framework for health and social care research. The trial is registered with the ClinicalTrials.gov trial registry (NCT04129970 and NCT04130906) and this protocol and related documents will be submitted for review to the Research Ethics Committee (REC). Protection of personal data will be guaranteed; all relevant EU legislation (e.g. Directive 95/46/EC) will be observed and respected. The Chief Investigator will submit a final report at the end of the trial to the funder, the REC and the Sponsor. The CI will ensure that REC Favourable Opinion, HRA approval, and SLaM Trust Confirmation of Capacity and Capability will be in place before recruiting from the Trust SLaM. Should it be necessary to add research sites at a later stage, the sponsor will be approached to review an amendment for submission to the HRA, and Confirmation of Capacity and Capability will be obtained from the new NHS sites before starting recruitment from research sites.

18. Quality Assurance

Monitoring of this trial to ensure compliance with Good Clinical Practice guidelines and scientific integrity will be managed by the study team through regular review of study procedures by the trial investigators.

19. Data Handling

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:

Participant data will be anonymised.

- All anonymised data will be stored electronically on a password protected computer.
- All trial data will be stored in line with the General Data Protection Regulation (GDPR) 2018.
- Hardcopies of participant-related data (e.g. GP letters) will be kept in locked cabinets at the Institute of Psychiatry, Psychology and Neuroscience, King's College London. Data will not be accessed by anyone other than members of the research team.

All trial data will be archived in line with Sponsor requirements.

20. Data Management

Questionnaire data will be collected using Qualtrics Survey Software and marked with participant identification numbers only. No identifiable information will be used when completing surveys on Qualtrics. Data will be stored in manual/paper files, and on university and laptop computers. There will be no personal data stored on laptop computers. Confidentiality and anonymity of all personal data will be retained throughout the entire study. Manual data files will be secured in a lockable filing cabinet at the section for eating disorders, King's College London IoPPN, and all electronic files will be password protected. Identifying information will be removed from the data and stored separately. Interviews will be audio recorded and transcribed by Michaela Flynn. Transcriptions will be pseudo-anonymised. All participants will be allocated a numeric code which will be used to identify their data. The master list of names which correspond to each participant's numeric identification code will be stored electronically and will be password protected. This information will only be accessed by key researchers involved in the study (Michaela Flynn, Professor Iain Campbell and Professor Ulrike Schmidt). In addition, participant consent forms will be securely stored in a locked filing cabinet at the section for eating disorders, King's College London IoPPN, which is not the same cabinet used to store pseudo-anonymised participant data (to ensure identifiable information cannot be matched to their unique participant code).

21. Publication Policy

The findings from this study will be included in an examined PhD thesis. It is also intended that the results of this study will be published in high-impact, peer-review journals and presented at national and international conferences. Research findings will also be disseminated to the lay audience through internal newsletters, the media (with the support of the IoPPN Communications team), social media (via accounts managed by the King's College London Eating Disorders Research Group), and publications prepared in collaboration with charitable organisations, e.g., Beat, the UK's leading eating disorder charity.

22. Insurance / Indemnity

Standard KCL insurance and NHS indemnity arrangements apply

23. Financial Aspects

Funding to conduct the trial is provided by the King's College London Post Graduate Research International Student Scholarship. The scholarship funding commenced October 2018, and comprises:

1. Tax-free stipend to the PhD student researcher of £16,777 per annum. The stipend is paid in 12 equal monthly instalments.
2. Research Training Support Grant (RTSG) to cover PhD research, dissemination and training costs: £20,000 (£5,000 per year for a maximum of 4 years).
3. Tuition Fees: £22,050 for 2018-2019 (King's College London full-time International Student ate). The 2019-2020 rate will be £23,000. Tuition fees for the 2020-2021 and 2021-2022 academic years may be subject to additional increases in line with King's terms and conditions.

Additional funding for this trial may come from the NIHR Maudsley BRC grant for research within the Obesity, Lifestyle and Learning from Extreme Phenotypes theme led by Professor Ulrike Schmidt.

24. Signatures

Ulrike Schmidt Date: 18/09/2019

Chief Investigator

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Appendix J.2. North West-Preston Research Ethics Committee Approval Letter

NHS
Health Research Authority

North West - Preston Research Ethics Committee
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0207 104 8197

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

04 May 2020

Professor Ulrike Schmidt
Head of Department for Psychological Medicine King's College London
King's College London
IoPPN
PO59, 16 De Crespigny Park
Camberwell
SE5 8AF

Dear Professor Schmidt

Study title:	**BITE: An integrated feasibility trial and case series of theta burst simulation in binge eating disorder**
REC reference:	**20/NW/0084**
Protocol number:	**N/A**
IRAS project ID:	**274241**

Thank you for your letter of 23 April 2020, 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 Chair.

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.

Conditions of the favourable opinion

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

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

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 management permissions from host organisations

Registration of Clinical Trials

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database. For this purpose, 'clinical trials' are defined as the first four project categories in IRAS project filter question 2. Registration is a legal requirement for clinical trials of investigational medicinal products (CTIMPs), except for phase I trials in healthy volunteers (these must still register as a condition of the REC favourable opinion).

Registration should take place as early as possible and within six weeks of recruiting the first research participant at the latest. Failure to register is a breach of these approval conditions, unless a deferral has been agreed by or on behalf of the Research Ethics Committee (see here for more information on requesting a deferral:
https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-research-project-identifiers/

As set out in the UK Policy Framework, research sponsors are responsible for making information about research publicly available before it starts e.g. by registering the research project on a publicly accessible register. Further guidance on registration is available at:
https://www.hra.nhs.uk/planning-and-improving-research/research-planning/transparency-responsibilities/

You should notify the REC of the registration details. We will audit these as part of the annual progress reporting process.

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).

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, including early termination of the study
- Final report

The latest guidance on these topics can be found at https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/.

Ethical review of research sites

NHS/HSC sites

The favourable opinion applies to all NHS/HSC sites listed in the application subject to confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or management permission (in Scotland) 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/HSC sites

I am pleased to confirm that the favourable opinion applies to any non-NHS/HSC sites listed in the application, subject to site management permission being obtained prior to the start of the study at the site.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [BITE Study Advertisement A4]	3	15 April 2020
Copies of advertisement materials for research participants [BITE Study Advertisement Postcard Size]	3	15 April 2020
Copies of advertisement materials for research participants [BITE Website Advertisement]	2	22 November 2019
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Evidence of Sponsors Insurance]	1	23 July 2019
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IRAS Application Form [IRAS_Form_29012020]		29 January 2020
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Letter from sponsor		27 January 2020
Non-validated questionnaire [Centre for Neuroimaging Sciences MRI Request Form]	1	18 September 2019
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Non-validated questionnaire [VAS Measure of Core Binge Eating Disorder Symproms]	1	18 September 2019
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Referee's report or other scientific critique report [PhD Upgrade Report Feedback on Proposed Study]		01 July 2019
Referee's report or other scientific critique report [PhD Project Approval Form]		24 May 2018
Research protocol or project proposal [BITE Study Protocol]	6	17 April 2020
Summary CV for Chief Investigator (CI) [CV for Professor Ulrike Schmidt]		21 June 2019
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Validated questionnaire [Clinical Impairment Assessment (Bohn & Fairburn, 2008)]		
Validated questionnaire [Positive and Negative Affect Schedule (PANAS; Walton et al., 1988)]		
Validated questionnaire [Delayed Gratification Inventory (Hoerger, Quirk & Weed, 2011)]		

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.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form

available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at:
https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS project ID: 274241	**Please quote this number on all correspondence**

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

Yours sincerely

Professor Karen Wright
Chair

Email:preston.rec@hra.nhs.uk

Enclosures: "After ethical review – guidance for researchers" *[SL-AR2]*

Copy to: Prof Reza Razavi

Appendix J.3. Health Research Authority Approval Letter

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Ulrike Schmidt
Head of Department for Psychological Medicine King's College London
King's College London IoPPN
PO59, 16 De Crespigny Park
Camberwell
SE5 8AF

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

05 June 2020

Dear Professor Schmidt

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**BITE: An integrated feasibility trial and case series of theta burst simulation in binge eating disorder**
IRAS project ID:	**274241**
Protocol number:	**6**
REC reference:	**20/NW/0084**
Sponsor	**King's College London**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **274241**. Please quote this on all correspondence.

Yours sincerely,

Michael Pate
Approvals specialist

Email: approvals@hra.nhs.uk

Copy to: *Prof Reza Razavi*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Copies of advertisement materials for research participants [BITE Study Advertisement A4]	3	15 April 2020
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Participant information sheet (PIS) [BITE Adult Participation Information Sheet]	8	22 May 2020
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Validated questionnaire [Delayed Gratification Inventory (Hoerger, Quirk & Weed, 2011)]		

IRAS project ID	274241

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
There is only one participating NHS organisation therefore there is only one site type	This is a single site study co-sponsored by the participating NHS organisation. You should work with your sponsor R&D office to make arrangements to set up the study. The sponsor R&D office will confirm to you when the study can start following issue of HRA and HCRW Approval.	This a non-commercial single site study taking place in the NHS where that single NHS organisation is also the study co-sponsor or associated academic institution through Joint Research office arrangements. If this study is subsequently extended to other NHS organisation(s) in England or Wales, an amendment should be submitted, with an Organisation information document and Schedule of Events for the newly participating NHS organisation(s) in England or Wales	Funding has been sought from Kings College London, additional funding for this trial may come from the NIHR Maudsley BRC grant for research.	A Principal Investigator should be appointed at study sites	No Honorary Research Contracts, Letters of Access or pre-engagement checks are expected for local staff employed by the participating NHS organisations. Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application would be expected to obtain a Letter of Access based on enhanced DBS checks and occupational health clearance.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio. Following REC favourable opinion, the information sheets were updated to bring them in line with GDPR requirements.