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Combining cognitive bias modification training (CBM) and transcranial direct current stimulation (tDCS) to treat binge eating disorder: study protocol of a randomised controlled feasibility trial

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Combining cognitive bias modification training (CBM) and transcranial direct current stimulation (tDCS) to treat binge eating disorder: study protocol of a randomised controlled feasibility trial

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ABSTRACT

Introduction: Binge Eating Disorder (BED) is a common mental disorder, closely associated with obesity. Existing treatments are only moderately effective with high relapse rates, necessitating novel interventions. This paper describes the rationale for, and protocol of, a feasibility randomised controlled trial (RCT), evaluating the combination of transcranial Direct Current Stimulation (tDCS) and a computerised cognitive training, namely Approach Bias Modification training (ABM), in patients with Binge Eating Disorder who are overweight or obese. The aim of this trial is to obtain information that will guide decision making and protocol development in relation to a future large-scale RCT of combined tDCS + ABM treatment in this group of patients, and also to assess the preliminary efficacy of this intervention. **Methods and analysis:** 66 participants with DSM-5 diagnosis of BED and a body mass index (BMI) of >25 kg/m² will be randomly allocated to one of 3 groups: ABM + real tDCS; ABM + sham tDCS or a control group. Participants in both intervention groups will receive 6 sessions of ABM + real/sham tDCS over 3 weeks; engaging in the ABM task while simultaneously receiving bilateral tDCS to the dorsolateral prefrontal cortex. ABM is based on an implicit learning paradigm in which participants are trained to enact an avoidance behaviour in response to visual food cues. Assessments will be conducted at baseline, post-treatment (3 weeks), and at follow-up (7 weeks post-randomisation). Feasibility outcomes assess recruitment and retention rates, acceptability of random allocation, blinding success (allocation concealment), completion of treatment sessions and research assessments. Other outcomes include eating disorder psychopathology and related neurocognitive outcomes (i.e. delay of gratification and inhibitory control), BMI, other psychopathology (i.e. mood), approach bias towards food, and surrogate endpoints (i.e. food cue reactivity, trait food craving, and food intake).

Ethics and dissemination: This study has been approved by the North West - Liverpool East Research Ethics Committee. Results will be published in peer-reviewed journals.

Trial registration number: ISRCTN35717198

Strengths and limitations of this study

- The ICARUS study is the first randomised controlled feasibility trial of multi-session transcranial Direct Current Stimulation (tDCS) combined with Cognitive Bias Modification training (CBM) for adults with Binge Eating Disorder.
- ICARUS will compare [tDCS + CBM] vs. [sham tDCS + CBM] and a wait-list control group.
- ICARUS is designed to answer questions about the efficacy of the treatments tested.
- Results would need to be replicated in a larger trial before recommendations for tDCS + CBM as a treatment adjunct for patients receiving outpatient treatment for BED can be made.

INTRODUCTION

Binge Eating Disorder (BED) is the most prevalent eating disorder (ED) worldwide, with 1-3% of the general population meeting diagnostic criteria[1,2]. Binge eating is a core symptom, characterised by consumption of large amounts of food, a sense of loss of control, and significant distress. Nearly 80% of those with lifetime BED have a comorbid psychiatric disorder, such as mood, anxiety, substance use disorders or another ED[2]. Due to the lack of compensatory behaviours (e.g. vomiting, excessive exercising), BED is often accompanied by, or leads to, obesity and associated physical complications[3,4]. In the general population, approximately 30-42% of people with BED are obese[2,5,6]. Around 30% of treatment-seeking obese people[7-9] and up to 47% of bariatric surgery candidates have full or partial BED[1,10,11]. Whilst BED itself has considerable individual and societal costs[12], the combination of BED and obesity is associated with more severe obesity, greater medical and psychiatric comorbidity, greater functional impairment and perinatal complications[12-15]. Treatments for BED and obesity are sub-optimally effective, with cognitive behavioural therapy (CBT) and some medications reducing binge eating and related psychopathology[1], and approximately 50-60% of patients achieving abstinence from bingeing at the end of treatment[18] with some sustained cessation at follow-up[19]. However, drop-out rates in established BED treatments reach 12-34%, and 30%-50% of BED patients relapse in long-term follow-ups[20-22], indicating that a substantial proportion do not maintain binge eating remission. Lisdexamfetamine[23] and topiramate[24] also reduce weight in the short-term but have considerable side effects[25], and their longer term efficacy is uncertain. Thus, there is a need for novel treatment developments.

The aetiology of BED is widely seen as multi-factorial. Emerging neurobiological models emphasise both the role of stress in the onset and maintenance of the disorder[26,27], and the development of addiction-like features; craving, tolerance and binge escalation over time[28,29], impulsivity and compulsivity, alterations in executive function and attention[30] and reward-related decision making[31].

Upon encountering images of high-calorie food, BED patients report enhanced reward sensitivity and exhibit stronger medial orbitofrontal cortex responses compared to healthy controls and participants with bulimia nervosa[32]. In individuals with obesity, who may or may not have BED, activation in the ventral striatum (part of the reward system) has been found to be higher compared to normal-weight controls [33], in tandem with a more pronounced approach bias towards appetising food images [34,35], leading to greater likelihood of consumption. Furthermore, poor reward-related decision making behaviour may be a maintaining factor in obesity[36]. Converging data using different methodologies, such as brain imaging, eye tracking, and behavioural test paradigms [37] have found that patients with BED demonstrate a higher arousal rate in response to food stimuli, a concurrent motor plan to start eating, a higher reward sensitivity, and greater inhibitory deficits as compared to individuals without BED[32,38,39]. Those with obesity and BED (compared to obesity alone) have demonstrated that their attentional bias to food images held higher motivational value[40], and responded more to high calorie food images in sites of cognitive planning of motor movements, driven by emotions, which may reflect impulsive tendencies in the face of a binge-eating trigger. This tendency to approach and consume palatable food items may thus be compounded by a greater sensitivity to reward and a decreased capacity to inhibit action tendencies. This is corroborated by the recent finding that individuals with BED or Bulimia Nervosa

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3 (BN) show higher food cue reactivity (increased cravings) when exposed to visual food cues
4 compared to healthy controls [41]. Such accumulating evidence of BED as a unique diagnostic group
5 situates it as a distinct phenotype within the obesity spectrum that is characterised by increased
6 impulsivity [42].
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10 Conventional treatments of BED, such as CBT may not be best suited to target highly automatic
11 cognitive processes that occur at an early stage in information processing and that are considered to
12 contribute to food craving and associated maladaptive cognitions/behaviours. Two “brain-directed”
13 treatments may provide an avenue for modifying these processes: Approach Bias Modification
14 training (ABM) and transcranial Direct Current Stimulation (tDCS).
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17 Approach Bias Modification training (ABM) is a form of cognitive bias modification training (CBM)
18 that aims to retrain approach bias tendencies (reach out towards) into avoidance ones (move away
19 from)[43] regarding stimuli such as appetitive cues. Participants are systematically trained to show
20 an avoidance movement in response to illness-related rewarding stimuli (e.g. food or alcohol) on a
21 computer screen. ABM techniques have shown potential in several pilot and large-scale randomised
22 controlled studies to treat alcohol[44] and tobacco[45] addictions, and to reduce consumption of
23 cannabis[46] and unhealthy foods[47,48]. ABM has also yielded promising results in people with high
24 levels of food craving and in bulimic eating disorders, including BED[49,50]. However, mixed results
25 in empirical studies across these domains[51,52] raise methodological issues of ABM studies to date,
26 such as low statistical power and suboptimal choice (or absence) of control groups[53] and
27 administration of single versus multiple training sessions.
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31 Transcranial Direct Current Stimulation (tDCS) is a form of non-invasive brain stimulation (NIBS) that
32 has been used as a treatment adjunct for a range of psychiatric disorders, such as depression,
33 schizophrenia and addictions[54–56]. Preliminary evidence suggests that tDCS and other forms of
34 non-invasive brain stimulation are promising tools to reduce food craving, ED symptoms and body
35 weight in bulimic EDs, including BED, and obesity[57]. Additionally, some studies indicate that NIBS
36 may reduce depression/stress levels and improve reward-based decision making in ED patients[58].
37 A frequent stimulation target is the dorsolateral prefrontal cortex (dlPFC) which plays a major role in
38 cognitive-inhibition, emotion regulation, and reward processing[58–61]. Although precise
39 mechanisms of action of tDCS have yet to be understood, a key hypothesis in relation to BED is that
40 enhancing dlPFC activity via tDCS alters the reward-cognition balance towards facilitation of
41 cognitive control and suppression of reward-related mechanisms driving food
42 craving/overeating[62].
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49 If given concurrently (i.e. ‘online training’), NIBS is reported to boost the effects of cognitive training
50 on the reduction of cognitive biases and the improvement of response inhibition[63]. NIBS may
51 enhance synaptic strength in neuronal pathways activated by cognitive training, amplifying effects of
52 training, and thus cognitive bias modification efficacy [64]. As the effectiveness of tDCS may thus be
53 improved by pairing administration with a cognitive task inducing activity in the target brain
54 region[65–67], such combined treatment interventions have been investigated among alcohol
55 dependent inpatients (ABM and tDCS)[68], and to enhance inhibitory control related to food
56 consumption (Go/No-Go Task and tDCS)[65]. The insignificant findings from these studies warrant
57 commentary that to date, studies that have found positive effects of tDCS have either included
58 obese participants or have had multisession protocols[65,69–71]. As this study incorporates both
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aspects, it is optimally designed to yield significant results.

In light of both the individual and societal burden incurred by the rising prevalence of BED and obesity, research interventions informing treatments that lead to stable and long-lasting remission are of critical importance. This research trial is the first to combine two promising novel intervention strategies in an integrated treatment and will yield important findings to shape future clinical trials. The intervention conditions of this feasibility study will involve 6 sessions of concurrent ABM and real or sham tDCS over 3 weeks, and will assess participant acceptability and dropout rates at this treatment frequency and duration. Additionally, the frequency of participants' ED symptoms and other outcomes related to general psychopathology and neurocognition will be measured before and after the study interventions to assess treatment success. In summary, this proof-of-concept and feasibility study will establish the utility of concurrent ABM + real tDCS in improving clinical outcomes in participants with BED, compared to ABM + sham tDCS, and a wait-list control group.

STUDY AIMS

In line with established recommendations for outcomes of feasibility trials[72], the primary aim is to assess the feasibility of using concurrent ABM + real tDCS compared to concurrent ABM + sham tDCS as an adjunct to treatment as usual (TAU) in this patient population, and acquire key information to inform the development of a large-scale randomised sham-controlled trial (RCT).

The specific objectives of the proposed feasibility study are to:

1. Establish the feasibility of conducting a large-scale RCT of ABM + tDCS in patients with BED by assessing recruitment, attendance, and retention rates;
2. Determine the practicality of administering both ABM and tDCS simultaneously;
3. Determine the best instruments for measuring outcomes in a full trial by examining the quality, completeness, and variability in the data;
4. Estimate the treatment effect sizes and standard deviations for outcome measures to inform the sample size calculation for a large-scale RCT;
5. Evaluate whether the treatment is operating as it is designed by analysing process measures, such as within-session visual analogue scales (VAS) of key ED symptoms;
6. Determine whether patients with BED evaluate concurrent ABM + tDCS as acceptable and credible;
7. Obtain information about patients' willingness to undergo random allocation to ABM paired with either real or sham tDCS administration, or the wait-list control condition.

A secondary aim is to investigate the potential efficacy of concurrent delivery of both forms of treatment on binge eating disorder.

This will involve evaluating if:

1. Concurrent sessions of ABM + real tDCS are superior to ABM + sham tDCS and to wait-list control in terms of frequency of objective binge eating episodes, food cue reactivity, food craving, food intake, eating disorder psychopathology and mood.
2. Concurrent ABM + tDCS is superior to the two other conditions in having an effect on the targeted neurocognitive mechanism (approach bias for high calorie food) and related neurocognitive parameters (i.e. impulsivity, delayed gratification, emotional regulation).

METHODS AND ANALYSIS

This study protocol has been written according to the SPIRIT statement (Standard Protocol Items for Randomised Trials)[73] and the CONSORT 2010 statement (Consolidated Standards of Reporting Trials)[72].

Study design

The ICARUS trial (Investigating Concurrent Approach Bias Modification Training and Transcranial Direct Current Stimulation in Binge Eating Disorder) is an exploratory randomised controlled feasibility trial with three parallel treatment conditions; ABM + real tDCS, ABM + sham tDCS and wait-list control. All participants across the two intervention groups will receive a treatment protocol of 6 sessions of ABM + real/sham tDCS conducted over 3 weeks. The comparator groups of a wait-list control and ABM + sham tDCS are necessary to evaluate the potential effect of real versus sham tDCS in participants with BED. The wait-list control group will be examined at the same time points to control for the possibility that improvements in the intervention groups are simply due to regression to the mean, spontaneous remission or other non-specific time effects. All participants will continue with TAU for their ED, and thus this selection of comparators is deemed acceptable. Within treatment session measures will involve visual analogues scales evaluating mood, stress and eating disorder symptoms. Assessments will be conducted 3 times during the study; at baseline, post-treatment (week 3), and at follow-up (week 7).

Participants

Inclusion criteria entail: (1) male and female community-dwelling adults (aged 18-70); (2) overweight or obese according to WHO criteria ($BMI > 25 \text{ kg/m}^2$)[74]; (3) a diagnosis of full-syndrome or sub-threshold Binge Eating Disorder according to the DSM-5[75]; (4) fluency in English; (5) normal or corrected to normal vision .

Exclusion criteria entail: (1) all known contraindications to tDCS[76]; (2) pregnancy; (3) a current significant/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) taking psychotropic medication other than a stable dosage of selective serotonin reuptake inhibitors (SSRI) for at least 14 days prior to study enrolment; (6) allergies to any of the foods presented in the study; (7) smoking >10 cigarettes per day; (8) drinking >3-4 units (men) or 2-3 units (women) of alcohol per day. In line with the CONSORT guidelines[77,78], we will record the number and reasons for any participants we must exclude, or any who decline consent or withdraw from the study.

Sample size

As ICARUS is a feasibility study, an a priori sample size 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[79,80]. We have chosen a target end sample size of $n=60$, (i.e. exceeds the upper end recommended for feasibility trials). However, assuming the attrition to follow-up rate is $a = 0.10$ (as found in previous eating disorder trials [81,82]) and applying an attrition correction factor of $1/(1-a)$, we will recruit an actual sample size of 66, i.e., 22 participants per group.

Randomisation

After the baseline assessment, participants will be allocated to one of three conditions at random to receive 6 sessions of either concurrent ABM + real tDCS or ABM + sham tDCS, or no intervention in the wait-list control condition. Participants in the wait-list control group will be offered the opportunity to receive ABM + real tDCS after the end of the follow-up. Participants will be individually randomised on a 1:1:1 ratio to the intervention or control groups in equal numbers. The generation and implementation of the randomisation sequence will be conducted independently from the trial team through a randomisation administrator who is not involved in any recruitment or research activity related to the ICARUS study. Online randomisation software (Sealed Envelope, London, UK) will be used for this purpose. Upon participant enrolment, the researcher will contact the randomisation administrator, who will inform this researcher in charge of carrying out the intervention of the participant's allocation via phone or email.

Blinding

Double blinding is implemented only for the intervention group cohorts of the trial. The research assessor will remain blind to each participant's tDCS assignment within the two intervention conditions until after the participant has completed the follow-up assessment. This double blinding protocol will be ensured via administration of the tDCS (NeuroConn DC-STIMULATOR PLUS) using "study mode". This involves a five-digit numerical code unique to each patient will be inputted into the device prior to the participant's testing session, that will initialise either sham or real (active) stimulation. The tDCS administrator and participants will remain blind to tDCS stimulation type throughout the study. Set-up of the randomisation codes and programming of the tDCS device will be performed by an investigator not involved in the trial. To assess blinding success, each participant and the researcher will be asked to guess the treatment allocation at the end of the 6 treatment sessions and to indicate how certain they are of this guess. The study group allocation will be revealed to the participant after their follow-up assessment. In the event of a reported change in a participant's medication, or a new clinical diagnosis made during their study participation, the early unblinding of study condition for an intervention group participant will be permissible. The trial database will be maintained 'blind' until the point of study data analyses.

Recruitment

The study will take place at the Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London (KCL), UK. Participants will be recruited from the Eating Disorders Service at the South London and Maudsley NHS Foundation Trust, from the KCL research recruitment webpage and social media account, and via posters placed on notice boards on KCL campuses. Participants who have previously taken part in research at the KCL Eating Disorders Unit and who have consented to be informed of future studies may also be contacted. The ICARUS study will also be advertised on the Beat (National Eating Disorders Association) website, callforparticipants.com and www.mqmentalhealth.org. Potential participants will receive written and verbal study information and will be screened for eligibility. Eligible participants will provide informed written consent for study participation as a prerequisite for enrolment (See Appendices B and C).

Procedure

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Figure 1 illustrates the timeline of the study procedures. All participants will partake in assessments at each of the three measurement points; baseline, post-treatment, and follow-up. Each assessment will comprise of an in-person study visit with tasks and measures, and online/hardcopy questionnaires and scales to be completed at home by the participant within 36 hours following the study visit. Table 1 details the tasks and measures allocated to each assessment and training visit. After the baseline assessment, participants are randomised to one of 3 groups; (1) ABM + real tDCS, (2) ABM + sham tDCS, or a waiting list control group (CG). Participants allocated to an intervention group will be offered 6 sessions of ABM + real/sham tDCS across 3 weeks. They may also receive TAU e.g. if they are currently engaged in outpatient treatment for their ED. The control group will not receive any study intervention, and may continue TAU during this 3 week period. The post-treatment assessment will be conducted on all participants after the 6th (final) session of ABM + real/sham tDCS for the intervention groups, and 3 weeks after the baseline assessment for the control group. The follow-up assessment will be conducted 28 days after the end of treatment, i.e. 7 weeks post-randomisation. A follow-up period is included because, if the effects of the intervention result from increased neuroplasticity, behavioural changes may need time to emerge. Assessing the longevity of favourable clinical outcomes beyond the treatment period is also relevant to the objectives of this feasibility study. The researcher conducting the assessment and testing sessions will remain blind to the study condition of intervention group participants until the follow-up has been completed.

Outcome assessment

Measures of feasibility, safety and adherence will be collected throughout the study. Outcomes related to ED symptoms, general psychopathology and neurocognition will be measured before and after the study intervention to assess treatment success. Each assessment session will be split into an in-person visit and at-home component to accommodate time constraints and minimise disruption to task performance due to participant fatigue. The in-person assessment measures will take approximately 75 minutes to complete, and the online questionnaires will take approximately 45 minutes.

Outcome Measures

Feasibility outcomes

As this is a feasibility study, an extensive range of outcome measures are included to help determine which are most sensitive to detecting a treatment effect. This will enable us to determine primary outcome(s) for a future large-scale RCT. However, based on previous research[49], the Eating Disorder Examination Questionnaire (EDE-Q) is anticipated to be a key outcome measure.

Intervention/service related outcomes

Feasibility outcomes include recruitment, attendance and retention rates, and acceptability of treatment by participants. Patients' acceptance of study interventions will be assessed by measuring treatment dropout rates and via the treatment tolerance and acceptability questionnaires. An interview assessment of treatment experience will be conducted with 20 participants after the follow-up is completed. 10 participants from each intervention group will be invited to provide

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3 feedback on their initial expectations and experiences of the ABM + real/sham tDCS treatments,
4 perceived strengths and weaknesses of the treatment they received, and suggestions for
5 improvements in procedures. Interviews will be recorded, transcribed and analysed using thematic
6 analysis. This will allow future studies to consider patients' feedback in the development of research
7 and clinical protocols of concurrent ABM and tDCS.
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10 *Clinical outcomes*

11 *Eating disorder and related psychopathology*

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13 (a) Eating Disorder Examination (EDE-Q)[83]: The EDE-Q is a widely used measure of eating-
14 disordered behaviour and is widely regarded as the instrument of choice for the assessment of EDs.
15 This will be administered at baseline, post-assessment and follow-up.
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19 b) Body Mass Index (BMI (kg/m²)): This assessment of body composition provides accurate
20 estimates of body fat percentages in adults, where sex and age are factored into the analysis
21 measuring height and weight[84]. To calculate BMI, height and weight measurements will be
22 obtained by the researcher at baseline, post-assessment and follow-up.
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25 (c) *Approach bias assessment tasks*

26 To identify the most sensitive method of assessing change in approach bias towards high-calorie
27 food items, two different computerised measures of approach bias will be used. In the Food
28 Approach-Avoidance Task (F-AAT)[85] participants are shown colour photographs of high-calorie,
29 palatable foods such as chocolate, cake, and pizza, and non-food household and office items such as
30 sponges and stationary on a computer-screen[86]. They are instructed to approach and avoid these
31 stimuli by moving a joystick toward themselves (approach) or away from themselves (avoidance). In
32 the Stimulus Response Compatibility Task (SRC)[87], participants perform a symbolic movement by
33 making a manikin image walk toward (approach) or away from stimuli (avoidance). See Appendix A
34 for more detailed information. Both of these tasks will be administered at baseline, post-assessment
35 and follow-up.
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40 (d) *Food choice attitudes/behaviour*

41 The Food Choice Task[88–90] is a computer-based paradigm that measures responses to images of
42 foods to assess food attitudes and characteristics of eating behaviour. Participants rate images of
43 food on a computer screen according to healthiness as well as tastiness. Based on these ratings they
44 are then offered a choice between a food that they consider "neutral" and a series of other foods.
45 See Appendix A for more detailed information. This task will be performed at baseline and post-
46 assessment.
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50 (e) *Food craving after cue exposure task*

51 The Food Challenge Task (FCT)[41] will be used to examine cue-induced food craving. In this task,
52 participants rate their state food craving using the Food Cravings Questionnaire State Version[91,92]
53 before and after being presented with a video on a computer screen of foods shown to be highly
54 appetising[93]. See Appendix A for more detailed information. This task will be performed at
55 baseline and post-assessment.
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60 (f) *Trait food craving*

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3 Three questionnaires will be used to comprehensively assess mechanisms implicated in trait food
4 craving. The Food Cravings Questionnaire Trait Version - reduced (FCQ-T-r)[94] is a 15 items only
5 reduced version of a self-report questionnaire that measures trait levels of craving for food. The 21-
6 item Power of Food Scale (PFS)[95] scale assesses the psychological influence of the mere presence
7 or availability of food. It measures appetite for, rather than consumption of, palatable foods, at
8 three levels of food proximity (food available, food present, and food tasted). The Yale Food
9 Addiction Scale Version 2.0 (YFAS 2.0)[96] reflects the current diagnostic understanding of addiction
10 to further investigate the potential role of an addictive process in problematic eating
11 behaviour[75,97–101]. See Appendix A for more detailed information. Each of these scales will be
12 administered at baseline, post-assessment and follow-up.
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17 *(g) Food intake in a bogus taste test[102]*

18 Participants will be instructed to rate and optionally consume highly palatable high-calorie food
19 items presented in 3 bowls. See Appendix A for more detailed information. This task will be
20 performed at baseline and post-assessment.
21
22

23
24 *(h) Increased preference for delayed rewards*

25 The Delay Discounting Task with Money and Food[103] examines whether small amounts of food
26 would be discounted more steeply than money, as occurs with larger amounts. See Appendix A for
27 more detailed information. This will be administered at baseline, post-assessment and follow-up.
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30
31 *(i) Inhibitory control*

32 The cued Go/No-Go computer task is a classic test of executive function, requiring effortful response
33 inhibition, and measures impulse control by the ability to inhibit instigated, prepotent responses. A
34 food specific go/no-go task[104] measures impulsivity and response inhibition with respect to food
35 and nonfood items. The Stop Signal Task (SST)[105] measures inhibitory control. Participants are
36 required to engage in a computer task but withhold their response in the presence of a stop signal.
37 An adaptation of the food version of the SST[106] will facilitate a comparison of responses between
38 food and non-food categories. See Appendix A for more detailed information. Both of these tasks
39 will be performed at baseline, post-assessment and follow-up.
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44 *Mood and emotion regulation*

45 The Emotion Regulation Questionnaire (ERQ)[107] is designed to measure respondents' tendency to
46 regulate their emotions regarding cognitive reappraisal and expressive suppression. The Positive and
47 Negative Affect Schedule (PANAS)[108] measures the degree of positive or negative affect
48 experienced "right now" in the current study. The Depression, Anxiety and Stress Scale (DASS-
49 21)[109] evaluates mood, anxiety and stress levels over the previous week. See Appendix A for more
50 detailed information. All of these measures will be administered at baseline, post-assessment and
51 follow-up.
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56 *Within session measures*

57 Within each training session, i.e. immediately before and after the ABM + real/sham tDCS procedure
58 the researcher will administer paper-based Visual Analogue Scales (VAS) assessing current hunger,
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3 feeling of fullness, urge to eat, urge to binge eat, feeling low, level of tension, level of stress, level of
4 anxiety, and any discomfort due to tDCS and ABM in the training session. See Appendix A for more
5 detailed information.
6

7 **Intervention**

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10 In both intervention groups participants will receive six sessions of concurrent ABM and real or sham
11 tDCS which will be delivered twice a week for three weeks. A researcher trained in tDCS
12 administration will deliver the training sessions.
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14 *Rationale for number of sessions:*

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16 Treatment parameters for interventions of ABM and tDCS separately in psychiatric disorder research
17 have not yet been standardised and vary from 1-12 sessions across a timeframe of days to multiple
18 weeks. Mixed results regarding optimal frequency of ABM sessions and related forms of cognitive
19 bias modification has been reported[110]. A maximum accumulative effect of modification efficacy
20 at 6 sessions has been found for approach bias modification for alcohol dependence[44]. While
21 there is a similar paucity of specifications for treatment parameters within tDCS, multisession NIBS
22 interventions are significantly more effective at reducing cravings and strengthening the ability to
23 refrain from food consumption than single session protocols in eating disorders and obesity[111]. As
24 a single session of tDCS on patients with BED was found to reduce craving and caloric intake[59], it
25 was hypothesised that repeated administration of tDCS would enhance this effect and may decrease
26 binge eating frequency.
27

28 *Within session safety procedures*

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31 The participant's blood pressure and heartrate will be taken by the researcher immediately before
32 and after the session. While the participant is comfortably seated, the tDCS and ABM will be
33 administered at the same time, i.e. participants will engage in ABM training whilst receiving tDCS.
34 Each session will last 20 minutes. The ABM training will start 5 minutes after the start of the brain
35 stimulation. ABM training will take place over 10 minutes and tDCS will then continue for a further 5
36 minutes. Participants will be reminded that they have the option to withdraw immediately and
37 terminate their participation in the study if they experience discomfort during tDCS administration,
38 or if they wish to withdraw for any reason that they may or may not wish to disclose.
39

40 *Approach bias modification training*

41
42
43 The ABM programme will use an implicit learning paradigm, based on a modified version of the Food
44 Approach/Avoidance Task (AAT)[85,112–114]. In this task, participants are shown pictures of food
45 and control (i.e. neutral office) items. They are required to pull (pictures grow bigger) or push
46 (pictures grow smaller) a joystick in response to the outer frame of the picture (round vs.
47 rectangular), irrespective of the picture content. The training version of the Food-AAT utilises an
48 implicit learning paradigm by presenting all food pictures in the "push" (i.e. avoid) format. The study
49 procedure for ABM administration is aligned with previous research[50,115].
50

51 *Transcranial direct current stimulation*

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54 TDCS (both real and sham) will be delivered using a NeuroConn® DC-STIMULATOR PLUS device at a
55 constant current of 2 mA (with a 10-second fade in/out) using two 25cm² surface sponge electrodes
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3 soaked in a sterile saline solution (0.9% sodium chloride). The anode will be placed over the right
4 dorsolateral prefrontal cortex (dlPFC) and the cathode over the left dlPFC. This montage has been
5 used in sham-controlled studies on food craving, bulimia nervosa and BED[59]. The stimulation site
6 will be located using the Beam F3 calculation method, which is based on the International 10-20
7 system. TDCS can occasionally result in mild discomfort during administration (i.e., tingling or itching
8 sensation, a slightly metallic taste, occasional redness at the site of the electrodes). Fatigue,
9 headache, nausea and insomnia have been reported as potential adverse reactions[116].
10 Participants who are at-risk for adverse effects[76] will be excluded from the study at the screening
11 stage.
12
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15 **Data analysis**

16
17 Data will be analysed with the Statistical Package of Social Sciences (SPSS). Feasibility outcome data
18 will be analysed with appropriate summary statistics. To determine quality, completeness, and
19 variability of the clinical outcome data, descriptive statistical analyses and graphical methods will be
20 used. Intent-to-treat analyses will be performed. The size of the treatment effect on each outcome
21 measure will be the difference in outcome data between those in the two treatment conditions and
22 control condition at post-assessment and follow-up. Group differences will be estimated using linear
23 mixed effects regression models, controlling for the baseline level of the outcome. The goal here is
24 not to determine significant group differences but to establish a suitably precise effect size for the
25 primary outcome at the post treatment assessment. This estimate will be used to guide the sample
26 size of a future efficacy trial. Correlational analyses may be computed to analyse relationships
27 between outcome variables and influences of potential covariates such as gender, age, BMI or
28 comorbidities. Outcome data already obtained for participants who discontinue or deviate from the
29 intervention protocol will be kept and analysed.
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35 **PATIENT AND PUBLIC INVOLVEMENT**

36
37 Patients and/or public were not involved in the study design process, however we will obtain 20
38 intervention participants' qualitative views on their treatment experience in this study to inform
39 future clinical trials.
40
41

42 **ETHICS AND DISSEMINATION**

43 **Data management and data monitoring**

44
45 Participant data will be anonymised and all anonymised data will be stored electronically on a
46 password protected computer at the IoPPN. All trial data will be stored in line with the General Data
47 Protection Regulation (GDPR) 2018. Hard copies of participant-related data (i.e. GP letters) will be
48 kept in locked cabinets at the IoPPN, King's College London. The final trial data set will not be
49 accessed by anyone other than members of the research team.
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53 Data will be stored on manual files, university and laptop computers. There will be no personal data
54 stored on laptop computers. Confidentiality and anonymity of all personal data will be retained
55 throughout the entire study. Manual files will be securely locked in a lockable filing cabinet, and all
56 electronic files will be password protected. Identifying information will be removed from the data,
57 stored separately and replaced with a numeric identification code. All participants will be allocated a
58 numeric code, which will be used to identify their data. The master list of names which correspond
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3 to each participant's numeric identification code will be stored electronically and will be password
4 protected. This information will only be accessible to key researchers involved in the study.
5

6 The online component of the assessment will use Online Surveys software (formerly BOS). King's
7 College London uses this software for large scale surveys, and it is fully compliant with UK data
8 protection laws. Participants will be emailed the link after the in-person component of each
9 assessment session, and instructed to complete the second online component of the assessment
10 within 36 hours. Participants will also have the option to receive and complete a hard copy version
11 of the questionnaires with a stamped addressed envelope to post back to the study researcher at
12 the IoPPN.
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16 It is intended that the results of this feasibility study will be reported and disseminated at national
17 and international conferences. Research findings may also be disseminated through internal
18 newsletters and publications in collaboration with Beat, the UK's largest eating disorder charity.
19

20 Owing to the size and nature of this small-scale feasibility study, a data monitoring committee was
21 not deemed to be required. There are no scheduled interim analyses and this trial may be
22 prematurely discontinued by the Chief Investigator on the basis of new safety information.
23
24

25 **Ethics and safety aspects**

26
27 This study has been approved by the North West - Liverpool East Research Ethics Committee. This
28 trial will be conducted in compliance with the study protocol, the Declaration of Helsinki, the
29 principles of good clinical practice (ICH-E6 guideline), the ICH-E8 guideline and the principles of GCP
30 and in accordance with all applicable regulatory requirements including but not limited to the UK
31 policy framework for health and social care research. The ICARUS trial is registered with the
32 International Standard Randomised Controlled Trial Number registry (number ISRCTN35717198). All
33 participants will be asked by the study researcher to provide written informed consent prior to
34 enrolment. Participants who are at-risk for adverse side effects^[76] will be excluded from the study at
35 the screening stage (i.e. such as those with pregnancy or epilepsy). Current safety parameters of
36 tDCS administration regarding voltage amplitude and duration of brain stimulation sessions will be
37 adhered to. Participants have the option to withdraw immediately and terminate their participation
38 in the study if they experience discomfort during tDCS administration, or if they wish to terminate
39 their participation for any other reason that they may or may not wish to disclose. After each
40 training session, participants will complete the tolerance, discomfort and side effects questionnaire
41 to report any adverse effects of the intervention training session. The researcher will record this
42 description of any reported adverse effects, and record the severity and duration of symptoms and
43 how the adverse effect was managed at the following training session. If a participant reports a new
44 clinical diagnosis or change in medication during their involvement in the study, a decision regarding
45 their continued participation in the study will be made by the research team and withdrawal of the
46 participant may be deemed necessary. Standard King's College London insurance and NHS indemnity
47 arrangements apply to this study. To promote study adherence, upon completion of the follow-up
48 assessment, each participant will be reimbursed for their time, efforts and travel (£60 for
49 assessments and up to £60 for travel expenses). Additionally, participants in the wait-list control
50 group will be offered the opportunity to receive 6 sessions of ABM + tDCS after the follow-up.
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DISCUSSION

The ICARUS study represents the first feasibility study that aims to exploit a synergistic therapeutic effect by combining two brain-directed interventions in a single treatment intervention for BED. The rising clinical need of individuals with BED is currently met with few available psychological and neuropharmacological treatment options[117]. Therefore, such research advancing the identification and validation of novel therapies is greatly warranted.

This paper delineates the protocol for a feasibility trial which will inform future studies (i.e., provide effect sizes for a large RCT) and contribute to the extant research advocating brain-directed interventions for BED. The protocol aligns with current parameters of tDCS administration used to treat BED and BN[58,59] and utilises a multitudes of measures to identify the most appropriate and sensitive tools to detect treatment induced changes across pathological and neurocognitive domains.

Pragmatic concerns related to the recruitment process entail ensuring a sufficient and consistent rate of participant enrollment to meet the target sample number within the allocated timeframe. Additionally, drop-out rates for CBT treatment among a BED cohort are moderately high (17–30%)[118], thus study adherence will need to be monitored, with a revision of incentives/ reimbursement if necessary. Participants who were randomly allocated to the wait list control may avail themselves of 6 sessions of ABM + real tDCS after they have completed the study, which may promote recruitment and participant retention. Documenting the management of these issues will help to inform the development of a future large-scale RCT of this combined treatment adjunct for BED.

To conclude, investigating novel treatments for BED is an imperative issue. Combining ABM with tDCS is the strategic amalgamation of two techniques that have already demonstrated therapeutic efficacy in their own right. This feasibility RCT will be the first to systematically assess the acceptability and efficacy of a noninvasive, safe and potentially effective treatment adjunct to other therapies, which will enhance the ability of healthcare services to provide optimal care to patients with BED.

Trial progress

Recruitment will commence in February 2018 and data collection is expected to be complete (including follow-up assessments) by April 2020. Any substantial protocol amendments will be communicated to investigators via email and to other parties as required. Amendments to the study protocol will be reported in publications reporting the study outcomes.

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3 **Contributors** GG, IC, US and TB were each involved in the study conception and design. GG drafted
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6
7

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10

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18
19

20 **Disclaimer** The views expressed are those of the author(s) and not necessarily those of the NHS, the
21 NIHR or the Department of Health.
22
23

24 **Competing interests** None declared
25

26 **Patient consent** Informed consent will be obtained by the researcher.
27

28 **Ethics approval** Ethical approval was given by the North West - Liverpool East Research Ethics
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30

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32

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34

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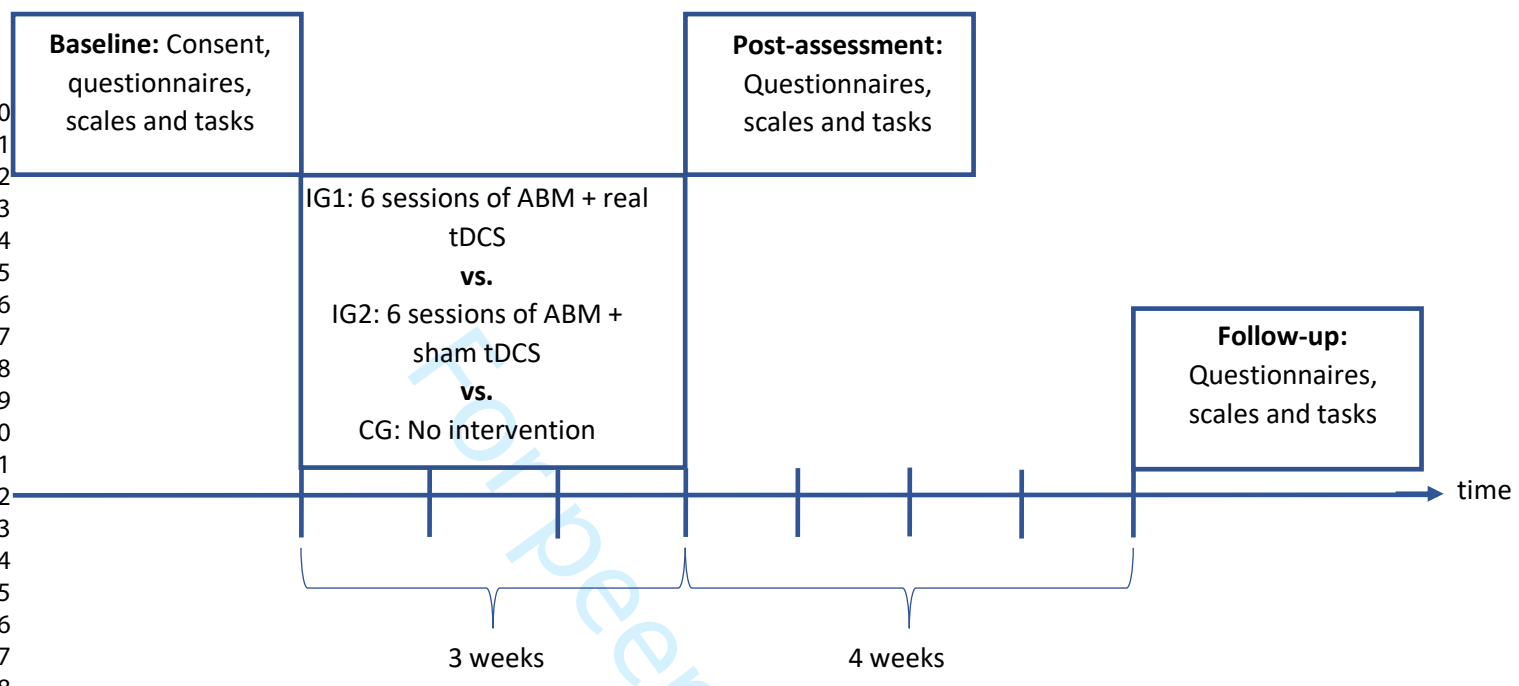
Figure 1 Study procedure. The 3 assessment time points are baseline, post-assessment and follow-up. IG1 is intervention group 1; IG2 is intervention group 2, CG is the wait list control group.

Table 1 Study schedule of measurement and testing time points

Approximate time since baseline	Screening of potential participants	Baseline assessment (all participants)	Training: 6 sessions of ABM + real tDCS 0-3 weeks	Training: 6 sessions of ABM + sham tDCS 0-3 weeks	Post-assessment (all participants) 3 weeks	Follow-up (all participants) 7 weeks
Informed consent		X				
EDDS, SCID-I	X					
TDCS safety screening	X					
Demographic information		X				
EDE-Q[83]		X			X	X
Inhibitory control tasks; Go/No-Go task[104], SST[106]		X			X	X
Delay Discounting Task with Money and Food[103]		X			X	X
Food related tasks; Food Choice Task[88], FCT, Bogus Taste Test[102]		X			X	
Approach bias assessment tasks; F-AAT[85], SRC[87]		X			X	X
Questionnaires & scales (incl. at home); EDRSQ[119], FCQ-T-r[94], PFS[95], YFAS 2.0[96], ERQ[107], PANAS[108], BIS-11[120], CIA[121], DGI[122], DASS-21[109]		X			X	X
Pre-[tDCS + ABM] measures: -Multiple VAS, blood pressure, pulse			X	X		
Real or sham tDCS to dLPFC			X	X		
Approach Bias Modification training			X	X		
Post-[tDCS + ABM] measures: -Multiple VAS, blood pressure, pulse			X	X		
Tolerance, discomfort and side effects			X	X		
Acceptability questionnaire						X
Blinding assessment questionnaire						X

EDDS; Eating Disorder Diagnostic Screen, SCID-I; Structured Clinical Interview for Diagnostic and Statistical Manual (DSM) Axis I Disorders, EDE-Q; Eating Disorder Examination, SST; Stop Signal Task, FCT; Food Challenge Task, F-AAT; Food Approach-Avoidance Task, SRC; Stimulus Response Compatibility Task, EDRSQ; Eating Disorder Recovery Self Efficacy Questionnaire, FCQ-T-r; Food Cravings Questionnaire Trait Version – reduced, PFS; The 21-item Power of Food Scale, YFAS 2.0; The Yale Food Addiction Scale Version 2.0, ERQ; Emotion Regulation Questionnaire, PANAS; Positive and Negative Affect Schedule, BIS-11; Barrett Impulsiveness Scale, CIA; Clinical Impairment Assessment, DGI; Delayed Gratification Inventory, DASS-21; Depression, Anxiety and Stress Scale.

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Supplementary File

Appendix A: ICARUS study task, questionnaire, measure and scale information

(1) Approach bias assessment tasks

(i) Food Approach-Avoidance Task (F-AAT) (Rinck & Becker, 2007): The F-AAT is a computerised task that measures approach and avoidance behaviour by means of joystick movements in response to food and neutral stimuli presented on a computer screen. This task will be used to assess approach bias towards visual cues of high-calorie food (expected target cognitive mechanism of intervention). Images of palatable edible foods (i.e. chocolate, pizza) and non-edible objects (i.e. sponges, stapler) are used as in previously (Brockmeyer et al., 2019). The assessment version of the AAT is identical to the treatment version except that the required response is unrelated to the picture content (i.e. food and neutral stimuli are presented equally often in round and rectangular, i.e. push and pull, format). Format movement assignments are counterbalanced among participants (i.e., half push round pictures and half push rectangular pictures). When the joystick is pulled, the picture grows bigger, and diminishes in size when the joystick is pushed. Zooming-in and zooming-out via joystick movements enacts motions of approaching and avoiding respectively and thus combines the proprioceptive (arm movement) and exteroceptive (zooming feature) cues of approach and avoidance behaviour (Neumann & Strack, 2000; Brockmeyer et al., 2019). The assessment version of the AAT consists of 80 trials (40 food item pictures and 40 non-food item pictures). To evaluate approach bias towards food, a compatibility score is calculated by subtracting the median reaction times (RTs) of compatible trials (i.e., RT pull food + RT push nonfood) from median RTs of incompatible trials (i.e., RT push food + RT pull nonfood) (Brockmeyer et al., 2019; Becker et al., 2016; Vrijssen et al., 2018). A positive value indicates a food-specific approach bias (i.e. the participant is faster at pulling than pushing food pictures, relative to the approach bias towards non-food), whereas a negative value indicates an avoidance bias. This task will be performed using Inquisit 5 (Millisecond Software).

(ii) The Stimulus Response Compatibility Task (SRC) (De Houwer, Crombez, Baeyens, & Hermans, 2001): In this task, participants respond to images on a computer screen by pressing keys on the keyboard. Pictures are presented in the centre of the screen with a manikin (12 mm high) positioned 33 mm above or below the picture. Participants are required to categorise the presented pictures by making an approach response (pressing the *up* or *down* key to move the manikin toward the picture) or an avoidance response (pressing the *up* or *down* key to move the manikin away from the picture). After making a correct response, an animation is shown of the manikin walking toward the picture (approach) or away from the picture (avoidance) for 1,000 ms. After making an incorrect response, a red cross appears on the screen for 500 ms, after which the next trial starts. Fourteen food and fourteen non-food pictures will be used from the food-pics database (Blechert, Meule, Busch & Ohla, 2014). The experiment comprises 8 practice trials and 56 experimental trials. Bias scores will be calculated by subtracting the mean of approach food/avoid non-food trials from the mean of avoid food/approach non-food trials. A positive score indicates a food-related approach bias, with higher scores indicative of stronger biases. This task will be performed using Inquisit 5 (Millisecond Software).

(2) Food Choice Task

The Food Choice Task (Hare, Camerer & Rangel., 2009) adapted for eating disorders (Steinglass et al., 2015) is a computer-based paradigm that measures responses to images of foods to assess food attitudes and characteristics of eating behaviour. Food stimuli is used to investigate how individuals make decisions about what to eat, and measures decision-making around food by directly probing personal preferences. There are no learning requirements and individualised assessments of food along two dimensions (healthiness and tastiness) allow the tasks to be used in diverse populations with differing valuations of food. The task consists of three phases. In each phase participants are presented with 43 images of food items. The food items represent an array of dietary options (Steinglass et al., 2015). Twenty-five food items are low fat (<30% calories from fat) and 18 are high fat (>30% calories from fat), as determined by Foerde et al. (2018). In the Health phase, participants rate the healthiness of each food item on a 5-point scale (1 = "Unhealthy", 5 = "Healthy"). In the Taste phase, participants rate the tastiness of each food item in a similar fashion, (1 = "Bad", 5 = "Good"). In the Choice phase, in each trial participants choose between the presented food item and a "Neutral" reference food item (rated as 3 in both Health and Taste phases). If no item is rated 3 on both scales, an item rated 3 on Health and greater than 3 on the Taste scale is selected as a reference food. Good test-retest reliability of the FCT suggests that it is suitable for measuring food-based decision-making in studies with multiple assessment points (Foerde et al., 2018).

(3) State food craving - Food craving after cue exposure task

The Food Challenge Task (FCT) (Kekic et al., 2017; Meule et al., 2018) 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 (Cepeda-Benito et al., 2000; Meule et al., 2012) before and after being presented with a video on a computer screen of foods shown to be highly appetising and to elevate hunger levels (Kekic et al., 2017). The questionnaire consists of 15 items that measure the strength of food cravings (i.e. *I would feel more alert if I could satisfy my craving*). Participants are asked to indicate how much they agree with each statement 'at this very moment' using a five-point scale (from 1 'strongly disagree' to 5 'strongly agree'). There are five craving subscales; intense desire to eat, anticipation of relief from negative states, physiological craving, preoccupation with food or lack of control over eating and anticipation of positive reinforcement. Scores can be calculated for specific subscales or a total score can be calculated (ranging from 15 to 75). This questionnaires will be completed using Inquisit 5 (Millisecond Software), and the video shown using QuickTime player.

(4) Trait food craving

The Yale Food Addiction Scale Version 2.0 (YFAS 2.0; Gearhardt, Corbin, & Brownell, 2016) is the most commonly used instrument to assess food-related addictive behaviours (Steward et al., 2018). This self-report questionnaire consists of 35 items scored on an 8-point Likert scale (from 0 = never to 7 = every day) and is adapted to assess addictive eating behaviours based on DSM-5 substance-related and addictive disorders criteria (APA, 2013). It refers specifically to consumption of foods high in fat, sugar, salt or refined carbohydrates. It

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3 includes items that assess specific criteria, such as diminished control over consumption, a
4 persistent desire or repeated unsuccessful attempts to quit, withdrawal, and clinically
5 significant impairment (i.e. *'I kept eating in the same way even though my eating caused*
6 *emotional problems'*). The YFAS includes two scoring options: 1) a "symptom count" ranging
7 from 0 to 7 that reflects the number of addiction-like criteria endorsed and 2) a categorical
8 scoring option that classifies respondents as having either no, mild, moderate or severe
9 'food addiction'. The YFAS has received psychometric support in binge eating populations
10 (Gearhardt, White et al., 2013; Carter, Van Wijk & Rowsell, 2019), and obese bariatric
11 surgery patients (Clark & Saules, 2013; Meule, Heckel, & Kübler, 2012). The YFAS 2.0 was
12 developed to maintain consistency with the current diagnostic understanding of addiction
13 and to improve the psychometric properties of the original YFAS. Exceeding the food
14 addiction threshold was more strongly associated with obesity for the YFAS 2.0 than the
15 original YFAS. The YFAS 2.0 has demonstrated good internal consistency (Carter, Van Wijk &
16 Rowsell, 2019), as well as convergent, discriminant and incremental validity (Gearhardt,
17 Corbin & Brownell, 2016).
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23 (5) *Food intake in a Bogus Taste Test*

24 Actual food consumption will be measured by means of a Bogus Taste Test (Robinson et al.,
25 2017); a food consumption test presented under the guise of a taste test. Participants will
26 be instructed to rate 3 bowls of highly palatable high-calorie food items (chocolate, sweets,
27 crisps) in terms of their visual attractiveness, smell, and taste on a paper form. The
28 researcher will inform the participant that she/he will leave the room for 10 minutes and
29 during this time they can complete their ratings and are free to eat as much of the offered
30 items as they like. A small bin with lid will be provided and participants will be instructed to
31 consume as much food as they need or want, and to discard the remainder of the food
32 items in the bin before 10 minutes are over. After the participant has left, the discarded
33 food items will be recovered from the bin, sorted, and placed in their original bowls.
34 Consumption will be determined by weighing the bowls both before and after the "taste
35 test" and the difference in weight from pre-to post-assessment will be converted into
36 calories and used as a measure of food intake.
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42 (6) *Delay discounting*

43 Delay Discounting Task with Money and Food (Odum, Baumann, & Rimington, 2006):
44 Participants indicate their preferences in a series of choices for two hypothetical outcome
45 types: immediate versus delayed food and immediate versus delayed money. Participants
46 make choices involving either relatively small maximum amounts of food (10 dollars worth)
47 and money (10 dollars) or for relatively large maximum amounts of food (100 dollars worth)
48 and money (100 dollars). Performance on this task can be used to study self-regulation,
49 delayed gratification and valuation of reward. This task will be performed using Inquisit 5
50 (Millisecond Software).
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54 (7) *Inhibitory control*

55 (i) *Go/No-Go task*: The cued go/no go task is a useful measure of impulse control in clinical
56 populations. This task is a classic test of executive function, requiring effortful response
57 inhibition. The food specific version of the cued go no-go task (Teslovich et al., 2014)
58 measures impulsivity and response inhibition with respect to appetising food and nonfood
59 items (i.e. toys), via assessing the ability to inhibit instigated, prepotent responses. The task
60

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 set of stimuli consists of 30 colour images of common high- (8) and low-calorie (7) foods and common toys (15). The outcome variables include: (1) overall reaction time (RT) in milliseconds during correct “go” trials, (2) rate of omission errors (missed “go” trials), and (3) false alarm rate (rate at which participants erroneously press to a no-go stimulus). This task will be performed using Inquisit 5 (Millisecond Software).

(i) Stop Signal Task (SST): This is a task measuring inhibitory control. Participants are required to engage in a computer task but withhold their response in the presence of a stop signal. This SST includes food-specific and neutral non-food stimuli in the same task (adaptation of Manasse et al., 2016). This allows for isolation of any unique food specific inhibitory control deficits from general difficulties inhibiting responses. The outcome measure is the stop signal reaction time (SSRT). The SSRT is calculated for each set of stimuli (i.e., SSRT stimulus type) for each subject by subtracting the average stop signal delay from the average reaction time on “go” trials (Verbruggen & Logan, 2008). The recording accuracy of reaction time and stop signal delay measurement is in milliseconds. A smaller SSRT is indicative of greater inhibitory control and a larger SSRT reflects weaker/impaired inhibitory control. This task will be performed using Inquisit 5 (Millisecond Software).

(8) Mood and emotion regulation

The Emotion Regulation Questionnaire (ERQ) (Gross & John, 2003): 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). This will be administered at pre-assessment, post-assessment and follow-up.

Positive and Negative Affect Schedule (PANAS) (Watson, Clarke & Tellegen, 1988): The PANAS consists of two 10-item self-report scales which measure positive and negative affect. On a Likert scale ranging from 0 (very slightly or not at all) to 4 (extremely), participants rate the extent to which they have experienced each of the 20 descriptors within a particular time frame (“right now” in the current study). Two scores are generated: positive (PANAS-positive) and negative (PANAS-negative) affect. This will be administered at pre-assessment, post-assessment and follow-up.

Depression, Anxiety and Stress Scale (21-item version; DASS-21) (Lovibond & Lovibond, 1995): This is a 21 item self-report questionnaire which aims to evaluate mood, anxiety and stress levels over the previous week. The DASS-21 will be administered at pre-assessment, post-assessment and follow-up.

(9) *Within session measures (immediately after each [ABM+real/sham tDCS] treatment session)*

(i) Paper-based Visual Analogue Scales (VAS) assessing current hunger, feeling of fullness, urge to eat, urge to binge eat, feeling low, level of tension, level of stress, level of anxiety. These scales consist of a 10cm line. Participants are requested to indicate on this line a degree or level of a specific emotion or behavioural urge. There are indications of what range (e.g. from 'not at all' to 'extremely').

(ii) Tolerance, discomfort and side effects: An evaluation of discomfort with the training session (tDCS and ABM aspects separately) will be completed with another paper-based 10cm VAS (rated from none to extreme discomfort). Participants will be asked to report any side effects in an open ended question.

Appendix B: Consent form for all participants

CONSENT FORM

IRAS Project ID: 244170

Research Ethics Committee reference number: 18/NW/0648

Please complete this form after you have read the information sheet and listened to an explanation about the research.



Title of Study: ICARUS - An Investigation of Approach Bias Modification Training (ABM) and Transcranial Direct Current Stimulation (tDCS) in Binge Eating Disorder
Name of Researcher: Gemma Gordon



Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the information sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this consent form to keep and refer to at any time.

Please initial box

1. I confirm that I have read the information sheet dated 18.09.2018 (version 3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected.
3. 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 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.

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4. I know that if I would like to, I can contact the research team and request a written summary of the study findings.
5. I understand that I must not take part if I have any of the conditions listed in the exclusion criteria.
6. I understand that during study participation, I must inform the researcher of any changes in my medication or of any new medical diagnoses made.
7. I agree to my General Practitioner (GP) being informed of my participation in this study.
8. I consent/do not consent to be contacted in the future by King's College London researchers who would like to invite me to participate in follow up studies to this project, or in future studies of a similar nature.
9. I agree to take part in the above study.

Participant's Statement:

I _____
agree that the research project named above has been explained to me to my satisfaction and I agree to take part in the study. I have read both the notes written above and the Information Sheet about the project, and understand what the research study involves.

Signed

Date

Investigator's Statement:

I _____
Confirm that I have carefully explained the nature, demands and any foreseeable risks (where applicable) of the proposed research to the participant.

Signed

Date

For administration purposes, please indicate your preference below

Q: In what format would you like to complete the at-home assessment questionnaires?

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2
3 Tick '✓' in one box to indicate your choice
4
5

6 1. I would like to complete the assessment questionnaires online

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8 2. I would like to receive a hardcopy paper version of the questionnaires in a
9 stamped addressed envelope, to complete and post back to the researcher within
10 36 hours of the in-person assessment visit.
11
12

13 **Enquiries:**

14 Gemma Gordon (gemma.gordon@kcl.ac.uk)
15 Department of Psychological Medicine
16 Section of Eating Disorders
17 KCL Institute of Psychology, Psychiatry and Neuroscience,
18 16 De Crespigny Park
19 London, SE5 8AF
20 Phone: 0207 848 5608
21
22
23

24 **Appendix C: Information sheet for all participants**

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27 **PARTICIPANT INFORMATION SHEET**

28 **ICARUS: An Investigation of Approach Bias Modification**
29 **Training (ABM) and Transcranial Direct Current**
30 **Stimulation (tDCS) in Binge Eating Disorder**
31
32



33 *IRAS Project ID: 244170*

34 *Research Ethics Committee reference number: 18/NW/0648*
35
36

37 We would like to invite you to participate in this postdoctoral research project which is being
38 conducted by a PhD student for research and educational purposes. You should only participate
39 if you want to; choosing not to take part will not disadvantage you in any way. Before you
40 decide whether you want to take part, it is important for you to understand why the research is
41 being done and what your participation will involve. Please take time to read the following
42 information carefully and discuss it with others if you wish. Part 1 tells you the purpose of this
43 study and what will happen to you if you take part. Part 2 gives you more detailed information
44 about the conduct of the study. Please ask us if there is anything that is not clear or if you would
45 like more information.
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49 **PART ONE**
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52 **What is the purpose of the study?**

53 Psychological therapy as a main treatment for Binge Eating Disorder (BED) may not be
54 effective for many people and may not be readily accessible in some areas. Medical
55 treatments for BED can have side effects and often do not remain effective in the long-
56 term. Therefore, there is an ongoing need for the development of new treatments.
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3 *Computerised approach bias modification training (ABM)* is a specific form of cognitive
4 bias modification (CBM) that has been used to successfully treat mental disorders such
5 as anxiety, depression, and addictive disorders. This technique involves several sessions
6 of computerised training, a procedure which has shown to be effective in reducing the
7 severity of some eating disorder symptoms in people with BED and Bulimia Nervosa
8 (BN). ABM works as such; automatic approach and avoidance tendencies towards food-
9 related cues are modified by repeated training of arm movements in front of a computer
10 screen. ABM has shown to reduce approach tendencies and attention towards food cues
11 in a subclinical sample of eating disorders involving binge eating, but its efficacy on
12 these features in people with full-syndrome eating disorders remains unclear. Further
13 research is needed to examine if ABM is effective in reducing the frequency of binge
14 eating episodes in people with BED.
15
16
17

18 *Transcranial direct current stimulation (tDCS)* is a non-invasive technique that is capable
19 of stimulating specific brain areas. Research shows that the frontal areas of the brain
20 play a role in the development and maintenance of eating disorders, including BED.
21 Stimulating these brain areas to alter their functioning is therefore believed to have the
22 potential to reduce eating disorder symptoms. This involves the delivery of a low
23 electrical current via small electrodes placed on the scalp. This procedure is widely used
24 in research and is being applied in clinical settings. Recent research using tDCS on
25 people with BED has suggested that it may be helpful in reducing immediate food intake
26 and cravings, and may decrease the frequency of a desire to binge eat at home after the
27 treatment.
28
29
30

31 ***Combining ABM and tDCS***

32 Previous studies suggest that these two techniques potentially help people better
33 regulate their behaviours through similar mechanisms in the brain. Delivering both
34 treatments together at the same time may have a stronger effect on reducing eating
35 disorder symptoms in people with BED than either of the treatments alone. This will be
36 the first time that this specific combination of interventions is conducted on people with
37 an eating disorder.
38
39

40
41 In the present study, we aim to investigate combined ABM and tDCS as a treatment for
42 BED by comparing the effect of 6 sessions of (ABM + real tDCS) vs. (ABM + placebo
43 tDCS) across a 3-week period in adult men and women with BED. We will also compare
44 these two groups against a control group. Participants will be allocated by chance to
45 either one of two intervention groups, or to the control group. Participants in the
46 intervention groups will receive 6 sessions of ABM delivered simultaneously with either
47 real tDCS or a placebo version of tDCS. Participants assigned to the control group will
48 not receive any intervention. We will measure eating disorder symptoms and other
49 outcomes in all participants at baseline, post-treatment, and at the 4-week follow-up to
50 assess outcomes of each study group. In particular, we are interested in changes in the
51 frequency of binge eating and craving, and thought processes and emotions related to
52 food and eating. We will also ask participants about their experience of this treatment.
53 Participants assigned to the control condition will be offered 6 sessions of (ABM + real
54 tDCS) after they have completed their involvement in the study.
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58 **Why have I been invited?**

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3 You are invited to participate if you are a male or female aged between 18 and 70 who
4 has a current diagnosis of binge eating disorder (BED). We will be recruiting 66
5 participants in total.
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8 **Do I have to take part?**

9 You do not have to take part in this experiment; it is your choice. If you decide to take
10 part, you will be asked to sign three identical consent forms. You will be free to
11 withdraw from the study at any time without giving a reason. Whether you decide to
12 take part or not will in no way influence your care or the timing of your treatment.
13
14

15 **What will happen to me if I take part and what will I have to do?**

16 If you decide you want to participate you will firstly be asked to engage in a telephone
17 conversation with the researcher (lasting approximately 20 minutes) to confirm that
18 you are eligible to take part. If you are, you will be invited to the Institute of Psychiatry,
19 Psychology and Neuroscience (Kings College London, Denmark Hill Campus) for a
20 baseline assessment session on a day that is convenient for both you and the researcher,
21 in either the morning or the afternoon. On this day, the researcher will discuss the study
22 with you in person, answer your questions, and if you are happy to take part, we will
23 ask you to sign three copies of a consent form: one for you to keep, one for us to keep,
24 and one that will be sent to your general practitioner (GP).
25
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28 This baseline assessment visit is longer than the treatment visits and is comprised of an
29 in-person visit and online questionnaires to complete at home. During the visit, you will
30 give informed study consent, complete two questionnaires, neuropsychological tasks
31 (brain puzzles), and a food task for which you will be asked to rate different foods. This
32 visit also involves an assessment version of the approach bias modification (ABM)
33 training programme, which is a computer based-task involving pushing and pulling a
34 joystick in response to shapes appearing on the computer screen. Weight and height
35 will be measured at each assessment, and participants may choose not to see the figures
36 recorded. Assessment visits will last 65-75 minutes. Within 36 hours after the in-person
37 visit, you will be emailed a link to a series of questionnaires (assessing mood and eating
38 disorder-related thoughts and habits) which will take 30-45 minutes to complete. There
39 is also the option to complete these assessment questionnaires in hardcopy paper
40 format.
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44 You will then be then randomised and informed of your randomly assigned study
45 condition within a week. If you are assigned to one of the two intervention conditions,
46 you will be asked to attend 6 sessions where you will perform the ABM task while
47 receiving either real or placebo tDCS, in addition to completing the post-treatment and
48 follow-up assessments. If you are assigned to the control group, you will not receive any
49 intervention, and will be asked to attend the post-treatment and follow-up assessments.
50
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53 All 6 intervention sessions will be identical and last approximately 40–50 minutes.
54 There is no need for any special preparation before the visits. Before and after each
55 intervention session, you will complete some scales related to aspects of your mood and
56 level of hunger. Your blood pressure and pulse will also be measured before and after
57 each intervention session to monitor your wellbeing.

58 During the (ABM + real/placebo tDCS) session you will sit on a comfortable chair facing
59 a computer screen, with a joystick on a table in front of you. You will wear a plastic
60

1
2
3 headband to keep the two tDCS electrodes in place (as shown in the diagram below).
4 The electrodes will be placed in small sponges soaked in a salt water solution, so they
5 might feel a bit wet against your head. The researcher will turn the machine on which
6 will deliver the currents. Depending on your assigned study condition, you will receive
7 real or placebo brain stimulation. The placebo session will be the same as the real
8 session, but the tDCS machine won't deliver any electrical current. Most people can't tell
9 the difference between real and placebo tDCS sessions.
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31 The tDCS will begin a few minutes prior to the start of the computer training
32 programme, to allow participants to become used to the sensation before starting the
33 ABM task on the computer. The training version of the ABM programme is a computer
34 based-task involving pushing and pulling a joystick in response to shapes appearing on
35 the computer screen. The tDCS will also continue for a few minutes after the ABM task
36 has ended. You will then be asked to rate any discomfort experienced during the session
37 due the tDCS.
38
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41 You will be asked to return to the Institute for 5 more identical intervention sessions
42 within 3 weeks, leaving a gap of at least 24 hours between each session. The post-
43 assessment will be conducted immediately after the 6th intervention session. This in-
44 person visit comprising of the final intervention session plus the post-assessment will
45 therefore last 90-120 minutes, with the online questionnaires to be completed within
46 36 hours after this visit (45 minutes). The follow-up assessment 4 weeks later will be
47 similar to the baseline assessment. This final visit will therefore take 75 minutes, with
48 the online questionnaires taking 45 minutes to complete at home afterwards.
49
50

51 20 participants (10 participants from each intervention condition) will be invited to
52 provide feedback on their experiences of study participation, initial expectations of the
53 intervention, perceived strengths and weaknesses, and suggestions for improvements
54 in an interview with the researcher. Declining this invitation to interview does not affect
55 study payment.
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58 6 months after the baseline assessment, participants may be contacted by phone by a
59 member of the King's College London Eating Disorders Unit for a brief phone call to
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3 evaluate the presence of eating disorder symptoms. This 6 month check-in will allow
4 any long-term therapeutic effects of the study treatment intervention to be evaluated.
5 Participation in this phone call will not affect participant payment, which will have been
6 administered earlier after the 1-month follow up assessment.
7
8

9 **Expenses and payments**

10 Upon completion of the study, all participants will be paid a maximum of £60 for
11 completing each of the three assessment sessions (comprised of an in-person visit and
12 at-home questionnaires); the baseline assessment, post-treatment assessment and
13 follow-up assessment (£20 each). This payment should be declared for tax and/or
14 benefit purposes. If you are assigned to an intervention condition involving 6 sessions
15 of brain stimulation and computer training, you may also be compensated up to £10 per
16 day for your travel expenses on these intervention session days.
17
18

19 **What is expected from you as a participant?**

20 We would expect you to complete all assessment sessions (pre-, post-treatment, follow-
21 up), and if you are randomised to an intervention group, to attend all 6 (ABM +
22 real/placebo tDCS) sessions as scheduled. We ask you to inform us immediately if for
23 any reason you suddenly find yourself unable to attend a scheduled session.
24
25

26 Please let us know of any health problem that has developed, or any new diagnosis
27 made since you enrolled for the study. Further, we would ask you to let us know of any
28 new medication or change in medication whilst you are taking part in the study.
29
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31 **What are the possible disadvantages and risks of taking part? What are the side effects?**

32 Combined brain stimulation and cognitive training sessions are time-consuming and
33 may cause fatigue from concentrating on the task.
34
35

36 TDCS has been shown to be safe when used correctly in a clinical setting. However, you
37 may find the procedure slightly uncomfortable. This is because a number of sensations
38 can occur beneath the electrodes during stimulation including tingling, pain, itching,
39 and burning. Not everyone feels these sensations or finds them uncomfortable, but if
40 you do, remember you are free to stop the study at any point without giving an
41 explanation. In some rarer cases, tDCS has been known to cause a headache, but this can
42 be treated with mild painkillers (e.g. paracetamol). No side effects of ABM are known.
43 We will assess any discomfort you may experience during intervention sessions
44 throughout your involvement in the trial.
45
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49 **What are the possible benefits of taking part?**

50 Unfortunately, there are no direct benefits to taking part in this study, but the
51 information we get may help us to improve the treatment of BED in the future.
52
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54 **What happens when the research study stops?**

55 When the research study stops, no further ABM + tDCS sessions will be available to
56 those who have received 6 sessions. Participants in the control group will have the
57 option of receiving 6 sessions of [ABM + real tDCS] once they have completed the
58 waiting period and follow-up assessment.
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3 Participants assigned to one of the intervention groups can request to be informed if
4 they had received ABM combined with real or placebo tDCS, once they have completed
5 the follow-up assessment.
6

7 **What if there is a problem?**

8 Any complaint about the way you have been dealt with during the study or any possible
9 harm you might suffer will be addressed. Detailed information on this is given in Part 2.
10
11

12 **Will my taking part in the study be kept confidential?**

13 Yes. We will follow ethical and legal practice and all information about you will be
14 handled in confidence. The details are included in Part 2.
15
16

17 *If the information in Part 1 has interested you and you are considering*
18 *participation, please read the additional information in Part 2 before making a*
19 *decision.*
20

21 **PART TWO**

22 **What if relevant and new information becomes available?**

23 Sometimes we get new information about the treatment being studied. This is not
24 expected to occur given the short time frame of participation (6 sessions across 3
25 weeks); however, if any new and relevant information becomes available during this
26 time we will inform you immediately. You can then decide whether you wish to
27 continue in the study.
28
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32 **What will happen if I don't want to carry on with the study?**

33 Your participation is voluntary and you do not have to take part in the study. You can
34 change your mind at any point and terminate your participation without giving a reason
35 to the researcher. You are free to withdraw from this study at any time without
36 consequence.
37
38

39 **Will participation in this study affect my routine healthcare, or the waiting period 40 for treatment for my eating disorder if I am currently on a waiting list?**

41 No. Participation in this study will have no impact on your treatment as usual, or
42 waiting time if you are currently awaiting treatment for your eating disorder. We fully
43 encourage you to begin treatment as provided by a health care professional as soon as it
44 becomes available to you. We simply ask that you inform us of any changes to your
45 treatment or medication while you are partaking in the study.
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48

49 **What if there is a problem?**

50 If you have a concern about any aspect of the study, please ask the researcher
51 (gemma.gordon@kcl.ac.uk, 0207 848 0183) who will do their best to answer your
52 questions.
53
54

55 **What if I wish to make a complaint?**

56 If you remain unhappy and wish to formally complain, complaints to the IoPPN should
57 be addressed to Dr Gill Dale. Director of Research Quality; Head, Joint R&D Office of
58 South London and Maudsley NHS Foundation Trust and Institute of Psychiatry,
59 Psychology & Neuroscience (IoPPN), P005, Institute of Psychiatry, Psychology &
60

1
2
3 Neuroscience (IoPPN), King's College London, De Crespigny Park, London SE5 8AF. NHS
4 complaints will follow NHS complaints procedures.
5

6 **Other sources of support for your eating disorder**

7
8 To access support and treatment, please see your Eating Disorders clinician or your GP
9 who will be able to advise you and refer you to the right service for you. You can also
10 obtain further information and support from www.beateatingdisorders.org.uk, the
11 national Eating Disorders charity.
12

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14 Should you wish to speak to someone outside of the university, please talk to your
15 Eating Disorders clinician, GP, the Beat helpline, and/or one of the study researchers
16 who is happy to liaise on your behalf if you so wish. The eating disorders charity Beat
17 provides helplines for adults and young people which offer support and information to
18 sufferers, carers and professionals. Further information can be found on their website
19 www.beateatingdisorders.org.uk, or by ringing their helpline 0808 801 0677.
20

21 **Will my taking part in the study be kept confidential?**

22
23 Your personal information and the data we collect from you will remain confidential at
24 all times. It will also remain anonymous to everyone apart from the primary
25 researchers. Manual files will be locked securely in a filing cabinet, which will be kept in
26 a locked office in the KCL Section of Eating Disorders, Department of Psychological
27 Medicine, IoPPN, and all electronic files will be password protected. All information
28 which is collected during the course of the research will be kept strictly confidential
29 according to the General Data Protection Regulation (GDPR), brought into effect on 25th
30 May, 2018. This new legislation creates some new rights for individuals to better reflect
31 data protection challenges in the modern digital age, as well as strengthening some of
32 the rights that currently exist under the Data Protection Act 1998.
33
34

35 **How will my personal data be used and what are my rights?**

36
37 King's College London is the sponsor for this study based in the United Kingdom. We
38 will be using information from you in order to undertake this study and will act as the
39 data controller for this study. This means that we are responsible for looking after your
40 information and using it properly. King's College London will keep identifiable
41 information about you for four years after the study has finished.
42

43 Your rights to access, change or move your information are limited, as we need to
44 manage your information in specific ways in order for the research to be reliable and
45 accurate. If you withdraw from the study, we will keep the information about you that
46 we have already obtained. To safeguard your rights, we will use the minimum
47 personally-identifiable information possible. You can find out more about how we use
48 your information by contacting the Study Coordinator Gemma Gordon.
49

50
51 KCL will use your name and contact details to contact you about the research study, and
52 make sure that relevant information about the study is recorded for your care, and to
53 oversee the quality of the study. Individuals from KCL and regulatory organisations may
54 look at your medical and research records to check the accuracy of the research
55 study. SLAM will pass these details to KCL along with the information collected from
56 you. The only people in KCL who will have access to information that identifies you will
57 be people who need to contact you regarding your participation or audit the data
58 collection process. The people who analyse the information will not be able to identify
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3 you and will not be able to find out your name or contact details. KCL will keep
4 identifiable information about you from this study for four years after the study has
5 finished.
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8 **Involvement of the General Practitioner (GP)**

9 As a matter of courtesy and in the interest of your wellbeing, we may let your GP know
10 about your participation in the study, and may request your permission to send them a
11 letter when you enroll. If you agree to this, you will be asked to provide us with your
12 GP's contact details so that we can send them a letter with details of the research.
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15 **Insurance/indemnity**

16 Standard KCL insurance and NHS indemnity arrangements apply.
17
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19 **Involvement of the insurance company**

20 If you have private medical insurance, you should inform your insurance company that
21 you are taking part in this study.
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23 **Will any genetic tests be done?**

24 No.
25
26

27 **What will happen to the results of the research study?**

28 You will be offered the opportunity to be informed about your individual results once
29 the data for all participants has been collected. If you want written feedback of the
30 study's findings you can contact the researcher (gemma.gordon@kcl.ac.uk) for a lay
31 summary. The results will be included in an examined postgraduate report, presented
32 as part of a postgraduate presentation, and sent to a medical journal for publication.
33 Your participation in the study will not be disclosed.
34
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36 **Who is organising and funding the research?**

37 This study is being funded by King's College London.
38
39

40 **Who has reviewed the study?**

41 All research in the NHS is looked at by an independent group of people, called a
42 Research Ethics Committee, to protect your interests. This study has been reviewed and
43 given favourable opinion by North West -Liverpool East Research Ethics Committee.
44
45

46 **Further information and contact details**

47 If you have any questions or require more information about this study, please contact
48 the researcher using the following contact details:

49 Gemma Gordon (gemma.gordon@kcl.ac.uk) (0207 848 5608)
50 Section of Eating Disorders, Department of Psychological Medicine
51 KCL Institute of Psychiatry, Psychology and Neuroscience,
52 16 De Crespigny Park
53 London, SE5 8AF
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____1_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_____1_____
Funding	4	Sources and types of financial, material, and other support	_____12_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____12_____
	5b	Name and contact information for the trial sponsor	_____12_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____12_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____11_____

1 **Introduction**

2

3 Background and rationale 6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention _____2-4____

4

5

6 6b Explanation for choice of comparators _____4____

7

8 Objectives 7 Specific objectives or hypotheses _____4____

9

10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) _____5____

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14 **Methods: Participants, interventions, and outcomes**

15

16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained _____6____

17

18

19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) _____5____

20

21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered _____9-10____

23

24

25 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) _____11____

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27 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) _____11____

28

29 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial _____4, 11____

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32 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended _____6-9____

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1	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	___6__
2				
3				
4	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___5__
5				
6				
7	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___11__
8				
9				

10 **Methods: Assignment of interventions (for controlled trials)**

11 Allocation:

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13				
14	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	___5-6__
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19				
20	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___6__
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24	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___5__
25				
26				
27	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___5__
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31		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___6__
32				
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35 **Methods: Data collection, management, and analysis**

36				
37	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___6-8__
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1		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____10-11_____
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4	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____10-11_____
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8	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____10_____
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11		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____10_____
12				
13		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____10_____
14				
15				
16				
17	Methods: Monitoring			
18				
19	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____10_____
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25		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____11_____
26				
27				
28	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____11_____
29				
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31	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____n/a_____
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35	Ethics and dissemination			
36				
37	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____1, 13_____
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1	Protocol	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____ 1, 12_____
2	amendments			
3				
4				
5	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ 12_____
6				
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8		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ n/a_____
9				
10				
11	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____ 10-11_____
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15	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____ 12_____
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18	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____ 10_____
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22	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____ 11_____
23				
24				
25	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____ 1, 11_____
26				
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29		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ 12_____
30				
31		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ n/a_____
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34	Appendices			
35				
36	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____ 24_____
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39	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____ n/a_____
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1 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
2 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
3 [“Attribution-NonCommercial-NoDerivs 3.0 Unported”](#) license.
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For peer review only



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1 (no results)
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2-4
	2b	Specific objectives or hypotheses	4-5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9-10
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	5
	7b	When applicable, explanation of any interim analyses and stopping guidelines	11
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5-6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5-6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	n/a
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	n/a
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	n/a
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	n/a
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	n/a
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	n/a
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	n/a
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	n/a
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	12

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming; for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Combining cognitive bias modification training (CBM) and transcranial direct current stimulation (tDCS) to treat binge eating disorder: study protocol of a randomised controlled feasibility trial

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Keywords:	Eating disorders < PSYCHIATRY, transcranial direct current stimulation, cognitive bias modification, binge eating, treatment

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Combining cognitive bias modification training (CBM) and transcranial direct current stimulation (tDCS) to treat binge eating disorder: study protocol of a randomised controlled feasibility trial

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Gemma Gordon¹, Timo Brockmeyer², Ulrike Schmidt¹, Iain Campbell¹

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Key words: cognitive bias modification, transcranial direct current stimulation, eating disorders, binge eating, treatment

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ABSTRACT

Introduction: Binge Eating Disorder (BED) is a common mental disorder, closely associated with obesity. Existing treatments are only moderately effective with high relapse rates, necessitating novel interventions. This paper describes the rationale for, and protocol of, a feasibility randomised controlled trial (RCT), evaluating the combination of transcranial Direct Current Stimulation (tDCS) and a computerised cognitive training, namely Approach Bias Modification training (ABM), in patients with Binge Eating Disorder who are overweight or obese. The aim of this trial is to obtain information that will guide decision making and protocol development in relation to a future large-scale RCT of combined tDCS + ABM treatment in this group of patients, and also to assess the preliminary efficacy of this intervention. **Methods and analysis:** 66 participants with DSM-5 diagnosis of BED and a body mass index (BMI) of >25 kg/m² will be randomly allocated to one of 3 groups: ABM + real tDCS; ABM + sham tDCS or a waitlist control group. Participants in both intervention groups will receive 6 sessions of ABM + real/sham tDCS over 3 weeks; engaging in the ABM task while simultaneously receiving bilateral tDCS to the dorsolateral prefrontal cortex. ABM is based on an implicit learning paradigm in which participants are trained to enact an avoidance behaviour in response to visual food cues. Assessments will be conducted at baseline, post-treatment (3 weeks), and follow-up (7 weeks post-randomisation). Feasibility outcomes assess recruitment and retention rates, acceptability of random allocation, blinding success (allocation concealment), completion of treatment sessions and research assessments. Other outcomes include eating disorder psychopathology and related neurocognitive outcomes (i.e. delay of gratification and inhibitory control), BMI, other psychopathology (i.e. mood), approach bias towards food, and surrogate endpoints (i.e. food cue reactivity, trait food craving, and food intake).

Ethics and dissemination: This study has been approved by the North West - Liverpool East Research Ethics Committee. Results will be published in peer-reviewed journals.

Trial registration number: ISRCTN35717198

Strengths and limitations of this study

- The ICARUS study is the first randomised controlled feasibility trial of multi-session transcranial Direct Current Stimulation (tDCS) combined with Cognitive Bias Modification training (CBM) for adults with Binge Eating Disorder.
- ICARUS will compare [tDCS + CBM] vs. [sham tDCS + CBM] and a wait-list control group.
- ICARUS is designed to answer questions about the efficacy of the treatments tested.
- Results would need to be replicated in a larger trial before recommendations for tDCS + CBM as a treatment adjunct for patients receiving outpatient treatment for BED can be made.

INTRODUCTION

Binge Eating Disorder (BED) is the most prevalent eating disorder (ED) worldwide, with 1-3% of the general population meeting diagnostic criteria[1,2]. Binge eating is a core symptom, characterised by consumption of large amounts of food, a sense of loss of control, and significant distress. Nearly 80% of those with lifetime BED have a comorbid psychiatric disorder, such as mood, anxiety, substance use disorders or another ED[2]. Due to the lack of compensatory behaviours (e.g. vomiting, excessive exercising), BED is often accompanied by, or leads to, obesity and associated physical complications[3,4]. In the general population, approximately 30-42% of people with BED are obese[2,5,6]. Around 30% of treatment-seeking obese people[7–9] and up to 47% of bariatric surgery candidates have full or partial BED[1,10,11]. Whilst BED itself has considerable individual and societal costs[12], the combination of BED and obesity is associated with more severe obesity, greater medical and psychiatric comorbidity, greater functional impairment and perinatal complications[12–15]. Treatments for BED and obesity are sub-optimally effective, with cognitive behavioural therapy (CBT)[16] and some medications[17] reducing binge eating and related psychopathology[1], and approximately 50-60% of patients achieving abstinence from bingeing at the end of treatment[18] with some sustained cessation at follow-up[19]. However, drop-out rates in established BED treatments reach 12-34%, and 30%-50% of BED patients relapse in long-term follow-ups[20–22], indicating that a substantial proportion do not maintain binge eating remission. Lisdexamfetamine[23] and topiramate[24] also reduce weight in the short-term but have considerable side effects[25], and their longer term efficacy is uncertain. Thus, there is a need for novel treatment developments.

The aetiology of BED is widely seen as multi-factorial. Emerging neurobiological models emphasise both the role of stress in the onset and maintenance of the disorder[26,27], and the development of addiction-like features; craving, tolerance and binge escalation over time[28,29], impulsivity and compulsivity, alterations in executive function and attention[30] and reward-related decision making[31].

Upon encountering images of high-calorie food, BED patients report enhanced reward sensitivity and exhibit stronger medial orbitofrontal cortex responses compared to healthy controls and participants with bulimia nervosa[32]. In individuals with obesity, who may or may not have BED, activation in the ventral striatum (part of the reward system) has been found to be higher compared to normal-weight controls [33], in tandem with a more pronounced approach bias towards appetising food images [34,35], leading to greater likelihood of consumption. Furthermore, poor reward-related decision making behaviour may be a maintaining factor in obesity[36]. Converging data using different methodologies, such as brain imaging, eye tracking, and behavioural test paradigms [37] have found that patients with BED demonstrate a higher arousal rate in response to food stimuli, a concurrent motor plan to start eating, a higher reward sensitivity, and greater inhibitory deficits as compared to individuals without BED[32,38,39]. Those with obesity and BED (compared to obesity alone) have demonstrated that their attentional bias to food images held higher motivational value[40], and responded more to high calorie food images in sites of cognitive planning of motor movements, driven by emotions, which may reflect impulsive tendencies in the face of a binge-eating trigger. This tendency to approach and consume palatable food items may thus be compounded by a greater sensitivity to reward and a decreased capacity to inhibit action tendencies. This is corroborated by the recent finding that individuals with BED or Bulimia Nervosa

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3 (BN) show higher food cue reactivity (increased cravings) when exposed to visual food cues
4 compared to healthy controls [41]. Such accumulating evidence of BED as a unique diagnostic group
5 situates it as a distinct phenotype within the obesity spectrum that is characterised by increased
6 impulsivity [42].
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10 Conventional treatments of BED, such as CBT may not be best suited to target highly automatic
11 cognitive processes that occur at an early stage in information processing and that are considered to
12 contribute to food craving and associated maladaptive cognitions/behaviours. Two “brain-directed”
13 treatments may provide an avenue for modifying these processes: Approach Bias Modification
14 training (ABM) and transcranial Direct Current Stimulation (tDCS).
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17 Approach Bias Modification training (ABM) is a form of cognitive bias modification training (CBM)
18 that aims to retrain approach bias tendencies (reach out towards) into avoidance ones (move away
19 from)[43] regarding stimuli such as appetitive cues. Participants are systematically trained to show
20 an avoidance movement in response to illness-related rewarding stimuli (e.g. food or alcohol) on a
21 computer screen. ABM techniques have shown potential in several pilot and large-scale randomised
22 controlled studies to treat alcohol[44] and tobacco[45] addictions, and to reduce consumption of
23 cannabis[46] and unhealthy foods[47,48]. ABM has also yielded promising results in people with high
24 levels of food craving and in bulimic eating disorders, including BED[49,50]. However, mixed results
25 in empirical studies across these domains[51,52] raise methodological issues of ABM studies to date,
26 such as low statistical power and suboptimal choice (or absence) of control groups[53] and
27 administration of single versus multiple training sessions.
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31 Transcranial Direct Current Stimulation (tDCS) is a form of non-invasive brain stimulation (NIBS) that
32 has been used as a treatment adjunct for a range of psychiatric disorders, such as depression,
33 schizophrenia and addictions[54–56]. Preliminary evidence suggests that tDCS and other forms of
34 non-invasive brain stimulation are promising tools to reduce food craving, ED symptoms and body
35 weight in bulimic EDs, including BED, and obesity[57]. Additionally, some studies indicate that NIBS
36 may reduce depression/stress levels and improve reward-based decision making in ED patients[58].
37 A frequent stimulation target is the dorsolateral prefrontal cortex (dlPFC) which plays a major role in
38 cognitive-inhibition, emotion regulation, and reward processing[58–61]. Although precise
39 mechanisms of action of tDCS have yet to be understood, a key hypothesis in relation to BED is that
40 enhancing dlPFC activity via tDCS alters the reward-cognition balance towards facilitation of
41 cognitive control and suppression of reward-related mechanisms driving food
42 craving/overeating[62].
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49 If given concurrently (i.e. ‘online training’), NIBS is reported to boost the effects of cognitive training
50 on the reduction of cognitive biases and the improvement of response inhibition[63]. NIBS may
51 enhance synaptic strength in neuronal pathways activated by cognitive training, amplifying effects of
52 training, and thus cognitive bias modification efficacy [64]. As the effectiveness of tDCS may thus be
53 improved by pairing administration with a cognitive task inducing activity in the target brain
54 region[65–67], such combined treatment interventions have been investigated among alcohol
55 dependent inpatients (ABM and tDCS)[68], and to enhance inhibitory control related to food
56 consumption (Go/No-Go Task and tDCS)[65]. The insignificant findings from these studies warrant
57 commentary that to date, studies that have found positive effects of tDCS have either included
58 obese participants or have had multisession protocols[65,69–71]. As this study incorporates both
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aspects, it is optimally designed to yield significant results.

In light of both the individual and societal burden incurred by the rising prevalence of BED and obesity, research interventions informing treatments that lead to stable and long-lasting remission are of critical importance, and novel therapies may play a role in serving as adjuncts to treatment as usual, to enhance improvement in clinical outcomes obtained from engaging with eating disorder treatment services. This research trial is the first to combine two promising novel intervention strategies in an integrated treatment and will yield important findings to shape future clinical trials. The intervention conditions of this feasibility study will involve 6 sessions of concurrent ABM and real or sham tDCS over 3 weeks, and will assess participant acceptability and dropout rates at this treatment frequency and duration. Additionally, the frequency of participants' ED symptoms and other outcomes related to general psychopathology and neurocognition will be measured before and after the study interventions to assess treatment success. In summary, this proof-of-concept and feasibility study will establish the utility of concurrent ABM + real tDCS in improving clinical outcomes in participants with BED, compared to ABM + sham tDCS, and a wait-list control group.

STUDY AIMS

In line with established recommendations for outcomes of feasibility trials[72], which at present are supported by the National Institute for Health Research, the primary aim is to assess the feasibility of using concurrent ABM + real tDCS compared to concurrent ABM + sham tDCS as a potential adjunct to treatment as usual (TAU) in this patient population, and acquire key information to inform the development of a large-scale randomised sham-controlled trial (RCT).

The specific objectives of the proposed feasibility study are to:

1. Establish the feasibility of conducting a large-scale RCT of ABM + tDCS in patients with BED by assessing recruitment, attendance, and retention rates;
2. Determine the practicality of administering both ABM and tDCS simultaneously;
3. Determine the best instruments for measuring outcomes in a full trial by examining the quality, completeness, and variability in the data;
4. Estimate the treatment effect sizes and standard deviations for outcome measures to inform the sample size calculation for a large-scale RCT;
5. Evaluate whether the treatment is operating as it is designed by analysing process measures, such as within-session visual analogue scales (VAS) of key ED symptoms;
6. Determine whether patients with BED evaluate concurrent ABM + tDCS as acceptable and credible;
7. Obtain information about patients' willingness to undergo random allocation to ABM paired with either real or sham tDCS administration, or the wait-list control condition.

A secondary aim is to investigate the potential efficacy of concurrent delivery of both forms of treatment on binge eating disorder.

This will involve evaluating if:

1. Concurrent sessions of ABM + real tDCS are superior to ABM + sham tDCS and to wait-list control in terms of frequency of objective binge eating episodes, food cue reactivity, food craving, food intake, eating disorder psychopathology and mood.

2. Concurrent ABM + tDCS is superior to the two other conditions in having an effect on the targeted neurocognitive mechanism (approach bias for high calorie food) and related neurocognitive parameters (i.e. impulsivity, delayed gratification, emotional regulation).
3. Concurrent ABM and sham tDCS is superior to the waitlist control in eliciting therapeutic effects on the aforementioned clinical outcomes and neurocognitive mechanisms, yet demonstrates an efficacy level below that of concurrent ABM and real tDCS.

METHODS AND ANALYSIS

This study protocol has been written according to the SPIRIT statement (Standard Protocol Items for Randomised Trials)[73] and the CONSORT 2010 statement (Consolidated Standards of Reporting Trials)[72].

Study design

The ICARUS trial (Investigating Concurrent Approach Bias Modification Training and Transcranial Direct Current Stimulation in Binge Eating Disorder) is an exploratory randomised controlled feasibility trial with three parallel treatment conditions; ABM + real tDCS, ABM + sham tDCS and wait-list control. All participants across the two intervention groups will receive a treatment protocol of 6 sessions of ABM + real/sham tDCS conducted over 3 weeks. The comparator groups of a wait-list control and ABM + sham tDCS are necessary to evaluate the potential effect of real versus sham tDCS in participants with BED. The wait-list control group will be examined at the same time points to control for the possibility that improvements in the intervention groups are simply due to regression to the mean, spontaneous remission or other non-specific time effects. Any participants who are engaging in treatment for their ED will continue with TAU, and thus this selection of comparators is deemed acceptable. Within treatment session measures will involve visual analogues scales evaluating mood, stress and eating disorder symptoms. Assessments will be conducted 3 times during the study; at baseline, post-treatment (week 3), and at follow-up (week 7).

Participants

Inclusion criteria entail: (1) male and female community-dwelling adults (aged 18-70); (2) overweight or obese according to WHO criteria (BMI>25 kg/m²)[74]; (3) a diagnosis of full-syndrome or sub-threshold Binge Eating Disorder according to the DSM-5[75]; (4) fluency in English; (5) normal or corrected to normal vision .

Exclusion criteria entail: (1) all known contraindications to tDCS[76]; (2) pregnancy; (3) a current significant/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) taking psychotropic medication other than a stable dosage of selective serotonin reuptake inhibitors (SSRI) for at least 14 days prior to study enrolment; (6) allergies to any of the foods presented in the study; (7) smoking >10 cigarettes per day; (8) drinking >3-4 units (men) or 2-3 units (women) of alcohol per day. In line with the CONSORT guidelines[77,78], we will record the number and reasons for any participants we must exclude, or any who decline consent or withdraw from the study.

Sample size

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3 As ICARUS is a feasibility study, an a priori sample size calculation is not necessary. Rather, its aim is
4 to provide effect sizes on which future large-scale studies can be powered. Total sample sizes of
5 $n=24$ to $n=50$ have been recommended for feasibility trials with a primary outcome measured on a
6 continuous scale, mainly because estimates of the standard deviation for normally distributed
7 variables tend to stabilise around this size[79,80]. We have chosen a target end sample size of $n=60$,
8 (i.e. exceeds the upper end recommended for feasibility trials). However, assuming the attrition to
9 follow-up rate is $a = 0.10$ (as found in previous eating disorder trials [81,82]) and applying an attrition
10 correction factor of $1/(1-a)$, we will recruit an actual sample size of 66, i.e., 22 participants per group.
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15 **Randomisation**

16 After the baseline assessment, participants will be allocated to one of three conditions at random to
17 receive 6 sessions of either concurrent ABM + real tDCS or ABM + sham tDCS, or no intervention in
18 the wait-list control condition. Participants in the wait-list control group will be offered the
19 opportunity to receive ABM + real tDCS after the end of the follow-up. Participants will be
20 individually randomised on a 1:1:1 ratio to the intervention or control groups in equal numbers. The
21 generation and implementation of the randomisation sequence will be conducted independently
22 from the trial team through a randomisation administrator who is not involved in any recruitment or
23 research activity related to the ICARUS study. Online randomisation software (Sealed Envelope,
24 London, UK) will be used for this purpose. Upon participant enrolment, the researcher will contact
25 the randomisation administrator, who will inform this researcher in charge of carrying out the
26 intervention of the participant's allocation via phone or email.
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31 **Blinding**

32 Double blinding is implemented only for the intervention group cohorts of the trial. The research
33 assessor will remain blind to each participant's tDCS assignment within the two intervention
34 conditions until after the participant has completed the follow-up assessment. This double blinding
35 protocol will be ensured via administration of the tDCS (NeuroConn DC-STIMULATOR PLUS) using
36 "study mode". This involves a five-digit numerical code unique to each patient will be inputted into
37 the device prior to the participant's testing session, that will initialise either sham or real (active)
38 stimulation. The tDCS administrator and participants will remain blind to tDCS stimulation type
39 throughout the study. Set-up of the randomisation codes and programming of the tDCS device will
40 be performed by an investigator not involved in the trial. To assess blinding success, each participant
41 and the researcher will be asked to guess the treatment allocation at the end of the 6 treatment
42 sessions and to indicate how certain they are of this guess. The study group allocation will be
43 revealed to the participant after their follow-up assessment. In the event of a reported change in a
44 participant's medication, or a new clinical diagnosis made during their study participation, the early
45 unblinding of study condition for an intervention group participant will be permissible. The trial
46 database will be maintained 'blind' until the point of study data analyses.
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54 **Recruitment**

55 The study will take place at the Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's
56 College London (KCL), UK. Participants will be recruited from the Eating Disorders Service at the
57 South London and Maudsley NHS Foundation Trust, from the KCL research recruitment webpage and
58 social media account, and via posters placed on notice boards on KCL campuses. Participants who
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3 have previously taken part in research at the KCL Eating Disorders Unit and who have consented to
4 be informed of future studies may also be contacted. The ICARUS study will also be advertised on
5 the Beat (National Eating Disorders Association) website, callforparticipants.com and
6 www.mqmentalhealth.org. Potential participants will receive written and verbal study information
7 and will be screened for eligibility. Eligible participants will provide informed written consent for
8 study participation as a prerequisite for enrolment (See Appendices A and B).
9

11 Procedure

12
13 Figure 1 illustrates the timeline of the study procedures. All participants will partake in assessments
14 at each of the three measurement points; baseline, post-treatment, and follow-up. Each assessment
15 will comprise of an in-person study visit with tasks and measures, and online/hardcopy
16 questionnaires and scales to be completed at home by the participant within 36 hours following the
17 study visit. Table 1 details the tasks and measures allocated to each assessment and training visit.
18 After the baseline assessment, participants are randomised to one of 3 groups; (1) ABM + real tDCS,
19 (2) ABM + sham tDCS, or a waitlist control group (CG). Participants allocated to an intervention
20 group will be offered 6 sessions of ABM + real/sham tDCS across 3 weeks. All study participants may
21 receive TAU e.g. if they are currently engaged in outpatient treatment for their ED. The control
22 group will not receive any study intervention, and any participants receiving outpatient services
23 treatment for their ED will continue TAU during this 3 week period. The post-treatment assessment
24 will be conducted on all participants after the 6th (final) session of ABM + real/sham tDCS for the
25 intervention groups, and 3 weeks after the baseline assessment for the control group. The follow-up
26 assessment will be conducted 28 days after the end of treatment, i.e. 7 weeks post-randomisation. A
27 follow-up period is included because, if the effects of the intervention result from increased
28 neuroplasticity, behavioural changes may need time to emerge. Assessing the longevity of
29 favourable clinical outcomes beyond the treatment period is also relevant to the objectives of this
30 feasibility study. The researcher conducting the assessment and testing sessions will remain blind to
31 the study condition of intervention group participants until the follow-up has been completed.
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39 Outcome assessment

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41 Measures of feasibility, safety and adherence will be collected throughout the study. Outcomes
42 related to ED symptoms, general psychopathology and neurocognition will be measured before and
43 after the study intervention to assess treatment success. Each assessment session will be split into
44 an in-person visit and at-home component to accommodate time constraints and minimise
45 disruption to task performance due to participant fatigue. The in-person assessment measures will
46 take approximately 75 minutes to complete, and the online questionnaires will take approximately
47 45 minutes.
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51 Outcome Measures

52 Feasibility outcomes

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54 As this is a feasibility study, an extensive range of outcome measures are included to help determine
55 which are most sensitive to detecting a treatment effect. This will enable us to determine primary
56 outcome(s) for a future large-scale RCT. However, based on previous research[49], the Eating
57 Disorder Examination Questionnaire (EDE-Q) is anticipated to be a key outcome measure.
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Intervention/service related outcomes

Feasibility outcomes include recruitment, attendance and retention rates, and acceptability of treatment by participants. Patients' acceptance of study interventions will be assessed by measuring treatment dropout rates and via the treatment tolerance and acceptability questionnaires. An interview assessment of treatment experience will be conducted with 20 participants after the follow-up is completed. 10 participants from each intervention group will be invited to provide feedback on their initial expectations and experiences of the ABM + real/sham tDCS treatments, perceived strengths and weaknesses of the treatment they received, and suggestions for improvements in procedures. Interviews will be recorded, transcribed and analysed using thematic analysis. This will allow future studies to consider patients' feedback in the development of research and clinical protocols of concurrent ABM and tDCS.

Clinical outcomes

Eating disorder and related psychopathology

(a) Eating Disorder Examination (EDE-Q)[83]: The EDE-Q is a widely used measure of eating-disordered behaviour and is widely regarded as the instrument of choice for the assessment of EDs. This will be administered at baseline, post-assessment and follow-up.

b) Body Mass Index (BMI (kg/m²)): This assessment of body composition provides accurate estimates of body fat percentages in adults, where sex and age are factored into the analysis measuring height and weight[84]. To calculate BMI, height and weight measurements will be obtained by the researcher at baseline, post-assessment and follow-up.

(c) Approach bias assessment tasks

To identify the most sensitive method of assessing change in approach bias towards high-calorie food items, two different computerised measures of approach bias will be used. In the Food Approach-Avoidance Task (F-AAT)[85] participants are shown colour photographs of high-calorie, palatable foods such as chocolate, cake, and pizza, and non-food household and office items such as sponges and stationary on a computer-screen[86]. They are instructed to approach and avoid these stimuli by moving a joystick toward themselves (approach) or away from themselves (avoidance). In the Stimulus Response Compatibility Task (SRC)[87], participants perform a symbolic movement by making a manikin image walk toward (approach) or away from stimuli (avoidance). See Appendix C for more detailed information. Both of these tasks will be administered at baseline, post-assessment and follow-up.

(d) Food choice attitudes/behaviour

The Food Choice Task[88–90] is a computer-based paradigm that measures responses to images of foods to assess food attitudes and characteristics of eating behaviour. Participants rate images of food on a computer screen according to healthiness as well as tastiness. Based on these ratings they are then offered a choice between a food that they consider "neutral" and a series of other foods. See Appendix C for more detailed information. This task will be performed at baseline and post-assessment.

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3 (e) *Food craving after cue exposure task*

4 The Food Challenge Task (FCT)[41] will be used to examine cue-induced food craving. In this task,
5 participants rate their state food craving using the Food Cravings Questionnaire State Version[91,92]
6 before and after being presented with a video on a computer screen of foods shown to be highly
7 appetising[93]. See Appendix C for more detailed information. This task will be performed at
8 baseline and post-assessment.
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12 (f) *Trait food craving*

13 Three questionnaires will be used to comprehensively assess mechanisms implicated in trait food
14 craving. The Food Cravings Questionnaire Trait Version - reduced (FCQ-T-r)[94] is a 15 items only
15 reduced version of a self-report questionnaire that measures trait levels of craving for food. The 21-
16 item Power of Food Scale (PFS)[95] scale assesses the psychological influence of the mere presence
17 or availability of food. It measures appetite for, rather than consumption of, palatable foods, at
18 three levels of food proximity (food available, food present, and food tasted). The Yale Food
19 Addiction Scale Version 2.0 (YFAS 2.0)[96] reflects the current diagnostic understanding of addiction
20 to further investigate the potential role of an addictive process in problematic eating
21 behaviour[75,97–101]. See Appendix C for more detailed information. Each of these scales will be
22 administered at baseline, post-assessment and follow-up.
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28 (g) *Food intake in a bogus taste test*

29 During the bogus taste test[102], participants will be instructed to rate and optionally consume
30 highly palatable high-calorie food items presented in 3 bowls. See Appendix C for more detailed
31 information. This task will be performed at baseline and post-assessment.
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34 (h) *Increased preference for delayed rewards*

35 The Delay Discounting Task with Money and Food[103] examines whether small amounts of food
36 would be discounted more steeply than money, as occurs with larger amounts. See Appendix C for
37 more detailed information. This will be administered at baseline, post-assessment and follow-up.
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40 (i) *Inhibitory control*

41 The cued Go/No-Go computer task is a classic test of executive function, requiring effortful response
42 inhibition, and measures impulse control by the ability to inhibit instigated, prepotent responses. A
43 food specific go/no-go task[104] measures impulsivity and response inhibition with respect to food
44 and nonfood items. The Stop Signal Task (SST)[105] measures inhibitory control. Participants are
45 required to engage in a computer task but withhold their response in the presence of a stop signal.
46 An adaptation of the food version of the SST[106] will facilitate a comparison of responses between
47 food and non-food categories. See Appendix C for more detailed information. Both of these tasks
48 will be performed at baseline, post-assessment and follow-up.
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53 *Mood and emotion regulation*

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55 The Emotion Regulation Questionnaire (ERQ)[107] is designed to measure respondents' tendency to
56 regulate their emotions regarding cognitive reappraisal and expressive suppression. The Positive and
57 Negative Affect Schedule (PANAS)[108] measures the degree of positive or negative affect
58 experienced "right now" in the current study. The Depression, Anxiety and Stress Scale (DASS-
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3 21)[109] evaluates mood, anxiety and stress levels over the previous week. See Appendix C for more
4 detailed information. All of these measures will be administered at baseline, post-assessment and
5 follow-up.
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8 *Within session measures*

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10 Within each training session, i.e. immediately before and after the ABM + real/sham tDCS procedure
11 the researcher will administer paper-based Visual Analogue Scales (VAS) assessing current hunger,
12 feeling of fullness, urge to eat, urge to binge eat, feeling low, level of tension, level of stress, level of
13 anxiety, and any discomfort due to tDCS and ABM in the training session. See Appendix C for more
14 detailed information.
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17 **Intervention**

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19 In both intervention groups participants will receive six sessions of concurrent ABM and real or sham
20 tDCS which will be delivered twice a week for three weeks. A researcher trained in tDCS
21 administration will deliver the training sessions.
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24 *Rationale for number of sessions:*

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26 Treatment parameters for interventions of ABM and tDCS separately in psychiatric disorder research
27 have not yet been standardised and vary from 1-12 sessions across a timeframe of days to multiple
28 weeks. Mixed results regarding optimal frequency of ABM sessions and related forms of cognitive
29 bias modification has been reported[110]. A maximum accumulative effect of modification efficacy
30 at 6 sessions has been found for approach bias modification for alcohol dependence[44]. While
31 there is a similar paucity of specifications for treatment parameters within tDCS, multisession NIBS
32 interventions are significantly more effective at reducing cravings and strengthening the ability to
33 refrain from food consumption than single session protocols in eating disorders and obesity[111]. As
34 a single session of tDCS on patients with BED was found to reduce craving and caloric intake[59], it
35 was hypothesised that repeated administration of tDCS would enhance this effect and may decrease
36 binge eating frequency.
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40 *Within session safety procedures*

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42 The participant's blood pressure and heartrate will be taken by the researcher immediately before
43 and after the session. While the participant is comfortably seated, the tDCS and ABM will be
44 administered at the same time, i.e. participants will engage in ABM training whilst receiving tDCS.
45 Each session will last 20 minutes. The ABM training will start 5 minutes after the start of the brain
46 stimulation. ABM training will take place over 10 minutes and tDCS will then continue for a further 5
47 minutes. Participants will be reminded that they have the option to withdraw immediately and
48 terminate their participation in the study if they experience discomfort during tDCS administration,
49 or if they wish to withdraw for any reason that they may or may not wish to disclose.
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54 *Approach bias modification training*

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56 The ABM programme will use an implicit learning paradigm, based on a modified version of the Food
57 Approach/Avoidance Task (AAT)[85,112–114]. In this task, participants are shown pictures of food
58 and control (i.e. neutral office) items. They are required to pull (pictures grow bigger) or push
59 (pictures grow smaller) a joystick in response to the outer frame of the picture (round vs.
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3 rectangular), irrespective of the picture content. The training version of the Food-AAT utilises an
4 implicit learning paradigm by presenting all food pictures in the “push” (i.e. avoid) format. The study
5 procedure for ABM administration is aligned with previous research[50,115].
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8 *Transcranial direct current stimulation*

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10 TDCS (both real and sham) will be delivered using a NeuroConn® DC-STIMULATOR PLUS device at a
11 constant current of 2 mA (with a 10-second fade in/out) using two 25cm² surface sponge electrodes
12 soaked in a sterile saline solution (0.9% sodium chloride). The anode will be placed over the right
13 dorsolateral prefrontal cortex (dlPFC) and the cathode over the left dlPFC. This montage has been
14 used in sham-controlled studies on food craving, bulimia nervosa and BED[59]. The stimulation site
15 will be located using the Beam F3 calculation method, which is based on the International 10-20
16 system. TDCS can occasionally result in mild discomfort during administration (i.e., tingling or itching
17 sensation, a slightly metallic taste, occasional redness at the site of the electrodes). Fatigue,
18 headache, nausea and insomnia have been reported as potential adverse reactions[116].
19 Participants who are at-risk for adverse effects[76] will be excluded from the study at the screening
20 stage.
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24 **Data analysis**

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26 Data will be analysed with the Statistical Package of Social Sciences (SPSS). Feasibility outcome data
27 will be analysed with appropriate summary statistics. To determine quality, completeness, and
28 variability of the clinical outcome data, descriptive statistical analyses and graphical methods will be
29 used. Intent-to-treat analyses will be performed. The size of the treatment effect on each outcome
30 measure will be the difference in outcome data between those in the two treatment conditions and
31 control condition at post-assessment and follow-up. Group differences will be estimated using linear
32 mixed effects regression models, controlling for the baseline level of the outcome. The goal here is
33 not to determine significant group differences but to establish a suitably precise effect size for the
34 primary outcome at the post treatment assessment. This estimate will be used to guide the sample
35 size of a future efficacy trial. Correlational analyses may be computed to analyse relationships
36 between outcome variables and influences of potential covariates such as demographic variables,
37 i.e. gender, age, BMI and clinical variables, i.e. start/stopping of psychotherapy, psychotropic
38 medication and presence of comorbidities. Outcome data already obtained for participants who
39 discontinue or deviate from the intervention protocol will be kept and analysed.
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46 **PATIENT AND PUBLIC INVOLVEMENT**

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48 Patients and/or public were not involved in the study design process, however we will obtain 20
49 intervention participants' qualitative views on their treatment experience in this study to inform
50 future clinical trials.
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52 **ETHICS AND DISSEMINATION**

53 **Data management and data monitoring**

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55 Participant data will be anonymised and all anonymised data will be stored electronically on a
56 password protected computer at the IoPPN. All trial data will be stored in line with the General Data
57 Protection Regulation (GDPR) 2018. Hard copies of participant-related data (i.e. GP letters) will be
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3 kept in locked cabinets at the IoPPN, King's College London. The final trial data set will not be
4 accessed by anyone other than members of the research team.
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6 Data will be stored on manual files, university and laptop computers. There will be no personal data
7 stored on laptop computers. Confidentiality and anonymity of all personal data will be retained
8 throughout the entire study. Manual files will be securely locked in a lockable filing cabinet, and all
9 electronic files will be password protected. Identifying information will be removed from the data,
10 stored separately and replaced with a numeric identification code. All participants will be allocated a
11 numeric code, which will be used to identify their data. The master list of names which correspond
12 to each participant's numeric identification code will be stored electronically and will be password
13 protected. This information will only be accessible to key researchers involved in the study.
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16
17 The online component of the assessment will use Online Surveys software (formerly BOS). King's
18 College London uses this software for large scale surveys, and it is fully compliant with UK data
19 protection laws. Participants will be emailed the link after the in-person component of each
20 assessment session, and instructed to complete the second online component of the assessment
21 within 36 hours. Participants will also have the option to receive and complete a hard copy version
22 of the questionnaires with a stamped addressed envelope to post back to the study researcher at
23 the IoPPN.
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26
27 It is intended that the results of this feasibility study will be reported and disseminated at national
28 and international conferences. Research findings may also be disseminated through internal
29 newsletters and publications in collaboration with Beat, the UK's largest eating disorder charity.
30

31 Owing to the size and nature of this small-scale feasibility study, a data monitoring committee was
32 not deemed to be required. There are no scheduled interim analyses and this trial may be
33 prematurely discontinued by the Chief Investigator on the basis of new safety information.
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36 **Ethics and safety aspects**

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38 This study has been approved by the North West - Liverpool East Research Ethics Committee. This
39 trial will be conducted in compliance with the study protocol, the Declaration of Helsinki, the
40 principles of good clinical practice (ICH-E6 guideline), the ICH-E8 guideline and the principles of GCP
41 and in accordance with all applicable regulatory requirements including but not limited to the UK
42 policy framework for health and social care research. The ICARUS trial is registered with the
43 International Standard Randomised Controlled Trial Number registry (number ISRCTN35717198). All
44 participants will be asked by the study researcher to provide written informed consent prior to
45 enrolment. Participants who are at-risk for adverse side effects[76] will be excluded from the study at
46 the screening stage (i.e. such as those with pregnancy or epilepsy). Current safety parameters of
47 tDCS administration regarding voltage amplitude and duration of brain stimulation sessions will be
48 adhered to. Participants have the option to withdraw immediately and terminate their participation
49 in the study if they experience discomfort during tDCS administration, or if they wish to terminate
50 their participation for any other reason that they may or may not wish to disclose. After each
51 training session, participants will complete the tolerance, discomfort and side effects questionnaire
52 to report any adverse effects of the intervention training session. The researcher will record this
53 description of any reported adverse effects, and record the severity and duration of symptoms and
54 how the adverse effect was managed at the following training session. If a participant reports a new
55 clinical diagnosis or change in medication during their involvement in the study, a decision regarding
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3 their continued participation in the study will be made by the research team and withdrawal of the
4 participant may be deemed necessary. Standard King's College London insurance and NHS indemnity
5 arrangements apply to this study. To promote study adherence, upon completion of the follow-up
6 assessment, each participant will be reimbursed for their time, efforts and travel (£60 for
7 assessments and up to £60 for travel expenses). Additionally, participants in the wait-list control
8 group will be offered the opportunity to receive 6 sessions of ABM + tDCS after the follow-up.
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12 13 **DISCUSSION**

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15 The ICARUS study represents the first feasibility study that aims to exploit a synergistic therapeutic
16 effect by combining two brain-directed interventions in a single treatment intervention for BED. The
17 rising clinical need of individuals with BED is currently met with few available psychological and
18 neuropharmacological treatment options[117]. Therefore, such research advancing the
19 identification and validation of novel therapies is greatly warranted.
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23 This paper delineates the protocol for a feasibility trial which will inform future studies (i.e., provide
24 effect sizes for a large RCT) and contribute to the extant research advocating brain-directed
25 interventions for BED. The protocol aligns with current parameters of tDCS administration used to
26 treat BED and BN[58,59] and utilises a multitudes of measures to identify the most appropriate and
27 sensitive tools to detect treatment induced changes across pathological and neurocognitive
28 domains.
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32 Pragmatic concerns related to the recruitment process entail ensuring a sufficient and consistent
33 rate of participant enrollment to meet the target sample number within the allocated timeframe.
34 Additionally, drop-out rates for CBT treatment among a BED cohort are moderately high (17–
35 30%)[118], thus study adherence will need to be monitored, with a revision of incentives/
36 reimbursement if necessary. Participants who were randomly allocated to the wait list control may
37 avail themselves of 6 sessions of ABM + real tDCS after they have completed the study, which may
38 promote recruitment and participant retention. Documenting the management of these issues will
39 help to inform the development of a future large-scale RCT of this combined treatment adjunct for
40 BED.
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45 To conclude, investigating novel treatments for BED is an imperative issue. Combining ABM with
46 tDCS is the strategic amalgamation of two techniques that have already demonstrated therapeutic
47 efficacy in their own right. This feasibility RCT will be the first to systematically assess the
48 acceptability and efficacy of a noninvasive, safe and potentially effective treatment adjunct to other
49 therapies, which will enhance the ability of healthcare services to provide optimal care to patients
50 with BED.
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54 **Trial progress**

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56 Recruitment will commence in February 2018 and data collection is expected to be complete
57 (including follow-up assessments) by April 2020. Any substantial protocol amendments will be
58 communicated to investigators via email and to other parties as required. Amendments to the study
59 protocol will be reported in publications reporting the study outcomes.
60

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Authorship policy No professional writers were involved in this study protocol, nor will be involved in the study report write-up.

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Disclaimer The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests None declared

Patient consent Informed consent will be obtained by the researcher.

Ethics approval Ethical approval was given by the North West - Liverpool East Research Ethics Committee (ref: 18/NW/0648).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Not applicable

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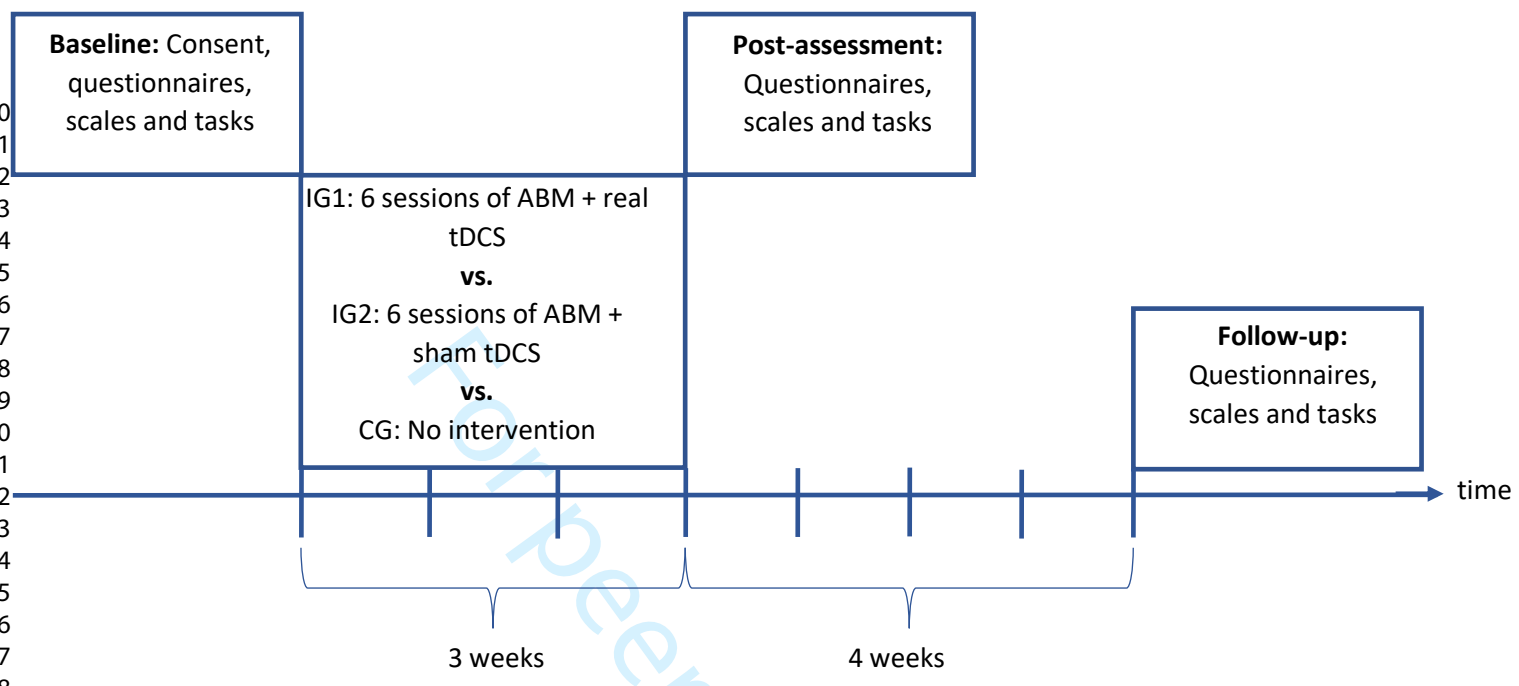
Figure 1 Study procedure. The 3 assessment time points are baseline, post-assessment and follow-up. IG1 is intervention group 1; IG2 is intervention group 2, CG is the wait list control group.

Table 1 Study schedule of measurement and testing time points

<u>Approximate time since baseline</u>	<u>Screening of potential participants</u>	<u>Baseline assessment (all participants)</u>	<u>Training: 6 sessions of ABM + real tDCS 0-3 weeks</u>	<u>Training: 6 sessions of ABM + sham tDCS 0-3 weeks</u>	<u>Post-assessment (all participants) 3 weeks</u>	<u>Follow-up (all participants) 7 weeks</u>
Informed consent		X				
EDDS, SCID-I	X					
TDCS safety screening	X					
Demographic information		X				
EDE-Q[83]		X			X	X
Inhibitory control tasks; Go/No-Go task[104], SST[106]		X			X	X
Delay Discounting Task with Money and Food[103]		X			X	X
Food related tasks; Food Choice Task[88], FCT, Bogus Taste Test[102]		X			X	
Approach bias assessment tasks; F-AAT[85], SRC[87]		X			X	X
Questionnaires & scales (incl. at home); EDRSQ[119], FCQ-T-r[94], PFS[95], YFAS 2.0[96], ERQ[107], PANAS[108], BIS-11[120], CIA[121], DGI[122], DASS-21[109]		X			X	X
Pre-[tDCS + ABM] measures: -Multiple VAS, blood pressure, pulse			X	X		
Real or sham tDCS to dLPFC			X	X		
Approach Bias Modification training			X	X		
Post-[tDCS + ABM] measures: -Multiple VAS, blood pressure, pulse			X	X		
Tolerance, discomfort and side effects			X	X		
Acceptability questionnaire						X
Blinding assessment questionnaire						X

BIS-11; Barrett Impulsiveness Scale, CIA; Clinical Impairment Assessment, DASS-21; Depression, Anxiety and Stress Scale, DGI; Delayed Gratification Inventory, EDDS; Eating Disorder Diagnostic Screen, EDE-Q; Eating Disorder Examination, EDRSQ; Eating Disorder Recovery Self Efficacy Questionnaire, ERQ; Emotion Regulation Questionnaire, FCQ-T-r; Food Cravings Questionnaire Trait Version – reduced, PANAS; Positive and Negative Affect Schedule, PFS; The 21-item Power of Food Scale, SCID-I; Structured Clinical Interview for Diagnostic and Statistical Manual (DSM) Axis I Disorders, SRC; Stimulus Response Compatibility Task, SST; Stop Signal Task, YFAS 2.0; The Yale Food Addiction Scale Version 2.0, .

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Supplementary File

Appendix A: Information sheet for all participants

PARTICIPANT INFORMATION SHEET**ICARUS: An Investigation of Approach Bias Modification Training (ABM) and Transcranial Direct Current Stimulation (tDCS) in Binge Eating Disorder**

IRAS Project ID: 244170

Research Ethics Committee reference number: 18/NW/0648

We would like to invite you to participate in this postdoctoral research project which 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. Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study. Please ask us if there is anything that is not clear or if you would like more information.

PART ONE

What is the purpose of the study?

Psychological therapy as a main treatment for Binge Eating Disorder (BED) may not be effective for many people and may not be readily accessible in some areas. Medical treatments for BED can have side effects and often do not remain effective in the long-term. Therefore, there is an ongoing need for the development of new treatments.

Computerised approach bias modification training (ABM) is a specific form of cognitive bias modification (CBM) that has been used to successfully treat mental disorders such as anxiety, depression, and addictive disorders. This technique involves several sessions of computerised training, a procedure which has shown to be effective in reducing the severity of some eating disorder symptoms in people with BED and Bulimia Nervosa (BN). ABM works as such; automatic approach and avoidance tendencies towards food-related cues are modified by repeated training of arm movements in front of a computer screen. ABM has shown to reduce approach tendencies and attention towards food cues in a subclinical sample of eating disorders involving binge eating, but its efficacy on these features in people with full-syndrome eating disorders remains unclear. Further research is needed to examine if ABM is effective in reducing the frequency of binge eating episodes in people with BED.

Transcranial direct current stimulation (tDCS) is a non-invasive technique that is capable of stimulating specific brain areas. Research shows that the frontal areas of the brain play a role in the development and maintenance of eating disorders, including BED. Stimulating these brain areas to alter their functioning is therefore believed to have the

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3 potential to reduce eating disorder symptoms. This involves the delivery of a low
4 electrical current via small electrodes placed on the scalp. This procedure is widely used
5 in research and is being applied in clinical settings. Recent research using tDCS on
6 people with BED has suggested that it may be helpful in reducing immediate food intake
7 and cravings, and may decrease the frequency of a desire to binge eat at home after the
8 treatment.
9

11 ***Combining ABM and tDCS***

12 Previous studies suggest that these two techniques potentially help people better
13 regulate their behaviours through similar mechanisms in the brain. Delivering both
14 treatments together at the same time may have a stronger effect on reducing eating
15 disorder symptoms in people with BED than either of the treatments alone. This will be
16 the first time that this specific combination of interventions is conducted on people with
17 an eating disorder.
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21 In the present study, we aim to investigate combined ABM and tDCS as a treatment for
22 BED by comparing the effect of 6 sessions of (ABM + real tDCS) vs. (ABM + placebo
23 tDCS) across a 3-week period in adult men and women with BED. We will also compare
24 these two groups against a control group. Participants will be allocated by chance to
25 either one of two intervention groups, or to the control group. Participants in the
26 intervention groups will receive 6 sessions of ABM delivered simultaneously with either
27 real tDCS or a placebo version of tDCS. Participants assigned to the control group will
28 not receive any intervention. We will measure eating disorder symptoms and other
29 outcomes in all participants at baseline, post-treatment, and at the 4-week follow-up to
30 assess outcomes of each study group. In particular, we are interested in changes in the
31 frequency of binge eating and craving, and thought processes and emotions related to
32 food and eating. We will also ask participants about their experience of this treatment.
33 Participants assigned to the control condition will be offered 6 sessions of (ABM + real
34 tDCS) after they have completed their involvement in the study.
35
36
37

38 **Why have I been invited?**

39 You are invited to participate if you are a male or female aged between 18 and 70 who
40 has a current diagnosis of binge eating disorder (BED). We will be recruiting 66
41 participants in total.
42
43

44 **Do I have to take part?**

45 You do not have to take part in this experiment; it is your choice. If you decide to take
46 part, you will be asked to sign three identical consent forms. You will be free to
47 withdraw from the study at any time without giving a reason. Whether you decide to
48 take part or not will in no way influence your care or the timing of your treatment.
49
50

51 **What will happen to me if I take part and what will I have to do?**

52 If you decide you want to participate you will firstly be asked to engage in a telephone
53 conversation with the researcher (lasting approximately 20 minutes) to confirm that
54 you are eligible to take part. If you are, you will be invited to the Institute of Psychiatry,
55 Psychology and Neuroscience (Kings College London, Denmark Hill Campus) for a
56 baseline assessment session on a day that is convenient for both you and the researcher,
57 in either the morning or the afternoon. On this day, the researcher will discuss the study
58 with you in person, answer your questions, and if you are happy to take part, we will
59
60

ask you to sign three copies of a consent form: one for you to keep, one for us to keep, and one that will be sent to your general practitioner (GP).

This baseline assessment visit is longer than the treatment visits and is comprised of an in-person visit and online questionnaires to complete at home. During the visit, you will give informed study consent, complete two questionnaires, neuropsychological tasks (brain puzzles), and a food task for which you will be asked to rate different foods. This visit also involves an assessment version of the approach bias modification (ABM) training programme, which is a computer based-task involving pushing and pulling a joystick in response to shapes appearing on the computer screen. Weight and height will be measured at each assessment, and participants may choose not to see the figures recorded. Assessment visits will last 65-75 minutes. Within 36 hours after the in-person visit, you will be emailed a link to a series of questionnaires (assessing mood and eating disorder-related thoughts and habits) which will take 30-45 minutes to complete. There is also the option to complete these assessment questionnaires in hardcopy paper format.

You will then be then randomised and informed of your randomly assigned study condition within a week. If you are assigned to one of the two intervention conditions, you will be asked to attend 6 sessions where you will perform the ABM task while receiving either real or placebo tDCS, in addition to completing the post-treatment and follow-up assessments. If you are assigned to the control group, you will not receive any intervention, and will be asked to attend the post-treatment and follow-up assessments.

All 6 intervention sessions will be identical and last approximately 40–50 minutes. There is no need for any special preparation before the visits. Before and after each intervention session, you will complete some scales related to aspects of your mood and level of hunger. Your blood pressure and pulse will also be measured before and after each intervention session to monitor your wellbeing. During the (ABM + real/placebo tDCS) session you will sit on a comfortable chair facing a computer screen, with a joystick on a table in front of you. You will wear a plastic headband to keep the two tDCS electrodes in place (as shown in the diagram below). The electrodes will be placed in small sponges soaked in a salt water solution, so they might feel a bit wet against your head. The researcher will turn the machine on which will deliver the currents. Depending on your assigned study condition, you will receive real or placebo brain stimulation. The placebo session will be the same as the real session, but the tDCS machine won't deliver any electrical current. Most people can't tell the difference between real and placebo tDCS sessions.



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7 The tDCS will begin a few minutes prior to the start of the computer training
8 programme, to allow participants to become used to the sensation before starting the
9 ABM task on the computer. The training version of the ABM programme is a computer
10 based-task involving pushing and pulling a joystick in response to shapes appearing on
11 the computer screen. The tDCS will also continue for a few minutes after the ABM task
12 has ended. You will then be asked to rate any discomfort experienced during the session
13 due the tDCS.
14
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16 You will be asked to return to the Institute for 5 more identical intervention sessions
17 within 3 weeks, leaving a gap of at least 24 hours between each session. The post-
18 assessment will be conducted immediately after the 6th intervention session. This in-
19 person visit comprising of the final intervention session plus the post-assessment will
20 therefore last 90-120 minutes, with the online questionnaires to be completed within
21 36 hours after this visit (45 minutes). The follow-up assessment 4 weeks later will be
22 similar to the baseline assessment. This final visit will therefore take 75 minutes, with
23 the online questionnaires taking 45 minutes to complete at home afterwards.
24
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26 20 participants (10 participants from each intervention condition) will be invited to
27 provide feedback on their experiences of study participation, initial expectations of the
28 intervention, perceived strengths and weaknesses, and suggestions for improvements
29 in an interview with the researcher. Declining this invitation to interview does not affect
30 study payment.
31
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33 6 months after the baseline assessment, participants may be contacted by phone by a
34 member of the King's College London Eating Disorders Unit for a brief phone call to
35 evaluate the presence of eating disorder symptoms. This 6 month check-in will allow
36 any long-term therapeutic effects of the study treatment intervention to be evaluated.
37 Participation in this phone call will not affect participant payment, which will have been
38 administered earlier after the 1-month follow up assessment.
39
40

41 **Expenses and payments**

42 Upon completion of the study, all participants will be paid a maximum of £60 for
43 completing each of the three assessment sessions (comprised of an in-person visit and
44 at-home questionnaires); the baseline assessment, post-treatment assessment and
45 follow-up assessment (£20 each). This payment should be declared for tax and/or
46 benefit purposes. If you are assigned to an intervention condition involving 6 sessions
47 of brain stimulation and computer training, you may also be compensated up to £10 per
48 day for your travel expenses on these intervention session days.
49
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51 **What is expected from you as a participant?**

52 We would expect you to complete all assessment sessions (pre-, post-treatment, follow-
53 up), and if you are randomised to an intervention group, to attend all 6 (ABM +
54 real/placebo tDCS) sessions as scheduled. We ask you to inform us immediately if for
55 any reason you suddenly find yourself unable to attend a scheduled session.
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3 Please let us know of any health problem that has developed, or any new diagnosis
4 made since you enrolled for the study. Further, we would ask you to let us know of any
5 new medication or change in medication whilst you are taking part in the study.
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8 **What are the possible disadvantages and risks of taking part? What are the side**
9 **effects?**

10 Combined brain stimulation and cognitive training sessions are time-consuming and
11 may cause fatigue from concentrating on the task.
12
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14 TDCS has been shown to be safe when used correctly in a clinical setting. However, you
15 may find the procedure slightly uncomfortable. This is because a number of sensations
16 can occur beneath the electrodes during stimulation including tingling, pain, itching,
17 and burning. Not everyone feels these sensations or finds them uncomfortable, but if
18 you do, remember you are free to stop the study at any point without giving an
19 explanation. In some rarer cases, tDCS has been known to cause a headache, but this can
20 be treated with mild painkillers (e.g. paracetamol). No side effects of ABM are known.
21 We will assess any discomfort you may experience during intervention sessions
22 throughout your involvement in the trial.
23
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25 **What are the possible benefits of taking part?**

26 Unfortunately, there are no direct benefits to taking part in this study, but the
27 information we get may help us to improve the treatment of BED in the future.
28
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30 **What happens when the research study stops?**

31 When the research study stops, no further ABM + tDCS sessions will be available to
32 those who have received 6 sessions. Participants in the control group will have the
33 option of receiving 6 sessions of [ABM + real tDCS] once they have completed the
34 waiting period and follow-up assessment.
35

36 Participants assigned to one of the intervention groups can request to be informed if
37 they had received ABM combined with real or placebo tDCS, once they have completed
38 the follow-up assessment.
39
40

41 **What if there is a problem?**

42 Any complaint about the way you have been dealt with during the study or any possible
43 harm you might suffer will be addressed. Detailed information on this is given in Part 2.
44
45

46 **Will my taking part in the study be kept confidential?**

47 Yes. We will follow ethical and legal practice and all information about you will be
48 handled in confidence. The details are included in Part 2.
49

50 ***If the information in Part 1 has interested you and you are considering***
51 ***participation, please read the additional information in Part 2 before making a***
52 ***decision.***
53

54
55 **PART TWO**
56
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58 **What if relevant and new information becomes available?**

59 Sometimes we get new information about the treatment being studied. This is not
60 expected to occur given the short time frame of participation (6 sessions across 3

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3 weeks); however, if any new and relevant information becomes available during this
4 time we will inform you immediately. You can then decide whether you wish to
5 continue in the study.
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8 **What will happen if I don't want to carry on with the study?**

9 Your participation is voluntary and you do not have to take part in the study. You can
10 change your mind at any point and terminate your participation without giving a reason
11 to the researcher. You are free to withdraw from this study at any time without
12 consequence.
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15 **Will participation in this study affect my routine healthcare, or the waiting period 16 for treatment for my eating disorder if I am currently on a waiting list?**

17 No. Participation in this study will have no impact on your treatment as usual, or
18 waiting time if you are currently awaiting treatment for your eating disorder. We fully
19 encourage you to begin treatment as provided by a health care professional as soon as it
20 becomes available to you. We simply ask that you inform us of any changes to your
21 treatment or medication while you are partaking in the study.
22
23

24 **What if there is a problem?**

25 If you have a concern about any aspect of the study, please ask the researcher
26 (gemma.gordon@kcl.ac.uk, 0207 848 0183) who will do their best to answer your
27 questions.
28
29

30 **What if I wish to make a complaint?**

31 If you remain unhappy and wish to formally complain, complaints to the IoPPN should
32 be addressed to Dr Gill Dale. Director of Research Quality; Head, Joint R&D Office of
33 South London and Maudsley NHS Foundation Trust and Institute of Psychiatry,
34 Psychology & Neuroscience (IoPPN), P005, Institute of Psychiatry, Psychology &
35 Neuroscience (IoPPN), King's College London, De Crespigny Park, London SE5 8AF. NHS
36 complaints will follow NHS complaints procedures.
37
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39 **Other sources of support for your eating disorder**

40 To access support and treatment, please see your Eating Disorders clinician or your GP
41 who will be able to advise you and refer you to the right service for you. You can also
42 obtain further information and support from www.beateatingdisorders.org.uk, the
43 national Eating Disorders charity.
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46 Should you wish to speak to someone outside of the university, please talk to your
47 Eating Disorders clinician, GP, the Beat helpline, and/or one of the study researchers
48 who is happy to liaise on your behalf if you so wish. The eating disorders charity Beat
49 provides helplines for adults and young people which offer support and information to
50 sufferers, carers and professionals. Further information can be found on their website
51 www.beateatingdisorders.org.uk, or by ringing their helpline 0808 801 0677.
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53

54 **Will my taking part in the study be kept confidential?**

55 Your personal information and the data we collect from you will remain confidential at
56 all times. It will also remain anonymous to everyone apart from the primary
57 researchers. Manual files will be locked securely in a filing cabinet, which will be kept in
58 a locked office in the KCL Section of Eating Disorders, Department of Psychological
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3 Medicine, IoPPN, and all electronic files will be password protected. All information
4 which is collected during the course of the research will be kept strictly confidential
5 according to the General Data Protection Regulation (GDPR), brought into effect on 25th
6 May, 2018. This new legislation creates some new rights for individuals to better reflect
7 data protection challenges in the modern digital age, as well as strengthening some of
8 the rights that currently exist under the Data Protection Act 1998.
9
10

11 **How will my personal data be used and what are my rights?**

12 King's College London is the sponsor for this study based in the United Kingdom. We
13 will be using information from you in order to undertake this study and will act as the
14 data controller for this study. This means that we are responsible for looking after your
15 information and using it properly. King's College London will keep identifiable
16 information about you for four years after the study has finished.
17

18 Your rights to access, change or move your information are limited, as we need to
19 manage your information in specific ways in order for the research to be reliable and
20 accurate. If you withdraw from the study, we will keep the information about you that
21 we have already obtained. To safeguard your rights, we will use the minimum
22 personally-identifiable information possible. You can find out more about how we use
23 your information by contacting the Study Coordinator Gemma Gordon.
24
25

26 KCL will use your name and contact details to contact you about the research study, and
27 make sure that relevant information about the study is recorded for your care, and to
28 oversee the quality of the study. Individuals from KCL and regulatory organisations may
29 look at your medical and research records to check the accuracy of the research
30 study. SLaM will pass these details to KCL along with the information collected from
31 you. The only people in KCL who will have access to information that identifies you will
32 be people who need to contact you regarding your participation or audit the data
33 collection process. The people who analyse the information will not be able to identify
34 you and will not be able to find out your name or contact details. KCL will keep
35 identifiable information about you from this study for four years after the study has
36 finished.
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40 **Involvement of the General Practitioner (GP)**

41 As a matter of courtesy and in the interest of your wellbeing, we may let your GP know
42 about your participation in the study, and may request your permission to send them a
43 letter when you enroll. If you agree to this, you will be asked to provide us with your
44 GP's contact details so that we can send them a letter with details of the research.
45
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48 **Insurance/indemnity**

49 Standard KCL insurance and NHS indemnity arrangements apply.
50

51 **Involvement of the insurance company**

52 If you have private medical insurance, you should inform your insurance company that
53 you are taking part in this study.
54
55

56 **Will any genetic tests be done?**

57 No.
58

59 **What will happen to the results of the research study?**

60

You will be offered the opportunity to be informed about your individual results once the data for all participants has been collected. If you want written feedback of the study's findings you can contact the researcher (gemma.gordon@kcl.ac.uk) for a lay summary. The results will be included in an examined postgraduate report, presented as part of a postgraduate presentation, and sent to a medical journal for publication. Your participation in the study will not be disclosed.

Who is organising and funding the research?

This study is being funded by King's College London.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by North West -Liverpool East Research Ethics Committee.

Further information and contact details

If you have any questions or require more information about this study, please contact the researcher using the following contact details:

Gemma Gordon (gemma.gordon@kcl.ac.uk) (0207 848 5608)
 Section of Eating Disorders, Department of Psychological Medicine
 KCL Institute of Psychiatry, Psychology and Neuroscience,
 16 De Crespigny Park
 London, SE5 8AF

Appendix B: Consent form for all participants

CONSENT FORM

IRAS Project ID: 244170

Research Ethics Committee reference number: 18/NW/0648

Please complete this form after you have read the information sheet and listened to an explanation about the research.

Title of Study: ICARUS - An Investigation of Approach Bias Modification Training (ABM) and Transcranial Direct Current Stimulation (tDCS) in Binge Eating Disorder

Name of Researcher: Gemma Gordon



Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the information sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this consent form to keep and refer to at any time.

Please initial box

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1. I confirm that I have read the information sheet dated 18.09.2018 (version 3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
 2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected.
 3. 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 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.
 4. I know that if I would like to, I can contact the research team and request a written summary of the study findings.
 5. I understand that I must not take part if I have any of the conditions listed in the exclusion criteria.
 6. I understand that during study participation, I must inform the researcher of any changes in my medication or of any new medical diagnoses made.
 7. I agree to my General Practitioner (GP) being informed of my participation in this study.
 8. **I consent/do not consent** to be contacted in the future by King's College London researchers who would like to invite me to participate in follow up studies to this project, or in future studies of a similar nature.
 9. I agree to take part in the above study.

44 **Participant's Statement:**

45
46
47 I _____
48 agree that the research project named above has been explained to me to my satisfaction
49 and I agree to take part in the study. I have read both the notes written above and the
50 Information Sheet about the project, and understand what the research study involves.
51

52
53 **Signed**

Date

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59 **Investigator's Statement:**

I _____
 Confirm that I have carefully explained the nature, demands and any foreseeable risks (where applicable) of the proposed research to the participant.

Signed **Date**

For administration purposes, please indicate your preference below

Q: In what format would you like to complete the at-home assessment questionnaires?

Tick '✓' in one box to indicate your choice

1. I would like to complete the assessment questionnaires online

2. I would like to receive a hardcopy paper version of the questionnaires in a stamped addressed envelope, to complete and post back to the researcher within 36 hours of the in-person assessment visit.

Enquiries:

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Appendix C: ICARUS study task, questionnaire, measure and scale information

(1) Approach bias assessment tasks

(i) Food Approach-Avoidance Task (F-AAT) (Rinck & Becker, 2007): The F-AAT is a computerised task that measures approach and avoidance behaviour by means of joystick movements in response to food and neutral stimuli presented on a computer screen. This task will be used to assess approach bias towards visual cues of high-calorie food (expected target cognitive mechanism of intervention). Images of palatable edible foods (i.e. chocolate, pizza) and non-edible objects (i.e. sponges, stapler) are used as in previously (Brockmeyer et al., 2019). The assessment version of the AAT is identical to the treatment version except that the required response is unrelated to the picture content (i.e. food and neutral stimuli are presented equally often in round and rectangular, i.e. push and pull, format). Format movement assignments are counterbalanced among participants (i.e., half push round pictures and half push rectangular pictures). When the joystick is pulled, the picture grows bigger, and diminishes in size when the joystick is pushed. Zooming-in and

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3 zooming-out via joystick movements enacts motions of approaching and avoiding
4 respectively and thus combines the proprioceptive (arm movement) and exteroceptive
5 (zooming feature) cues of approach and avoidance behaviour (Neumann & Strack, 2000;
6 Brockmeyer et al., 2019). The assessment version of the AAT consists of 80 trials (40 food
7 item pictures and 40 non-food item pictures). To evaluate approach bias towards food, a
8 compatibility score is calculated by subtracting the median reaction times (RTs) of
9 compatible trials (i.e., RT pull food + RT push nonfood) from median RTs of incompatible
10 trials (i.e., RT push food + RT pull nonfood) (Brockmeyer et al., 2019; Becker et al., 2016;
11 Vrijssen et al., 2018). A positive value indicates a food-specific approach bias (i.e. the
12 participant is faster at pulling than pushing food pictures, relative to the approach bias
13 towards non-food), whereas a negative value indicates an avoidance bias. This task will be
14 performed using Inquisit 5 (Millisecond Software).
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19 (ii) The Stimulus Response Compatibility Task (SRC) (De Houwer, Crombez, Baeyens, &
20 Hermans, 2001): In this task, participants respond to images on a computer screen by
21 pressing keys on the keyboard. Pictures are presented in the centre of the screen with a
22 manikin (12 mm high) positioned 33 mm above or below the picture. Participants are
23 required to categorise the presented pictures by making an approach response (pressing the
24 *up* or *down* key to move the manikin toward the picture) or an avoidance response (pressing
25 the *up* or *down* key to move the manikin away from the picture). After making a correct
26 response, an animation is shown of the manikin walking toward the picture (approach) or
27 away from the picture (avoidance) for 1,000 ms. After making an incorrect response, a red
28 cross appears on the screen for 500 ms, after which the next trial starts. Fourteen food and
29 fourteen non-food pictures will be used from the food-pics database (Blechert, Meule,
30 Busch & Ohla, 2014). The experiment comprises 8 practice trials and 56 experimental trials.
31 Bias scores will be calculated by subtracting the mean of approach food/avoid non-food
32 trials from the mean of avoid food/approach non-food trials. A positive
33 score indicates a food-related approach bias, with higher scores indicative of stronger
34 biases. This task will be performed using Inquisit 5 (Millisecond Software).
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41 (2) Food Choice Task

42 The Food Choice Task (Hare, Camerer & Rangel., 2009) adapted for eating disorders
43 (Steinglass et al., 2015) is a computer-based paradigm that measures responses to images of
44 foods to assess food attitudes and characteristics of eating behaviour. Food stimuli is used
45 to investigate how individuals make decisions about what to eat, and measures decision-
46 making around food by directly probing personal preferences. There are no learning
47 requirements and individualised assessments of food along two dimensions (healthiness
48 and tastiness) allow the tasks to be used in diverse populations with differing valuations of
49 food. The task consists of three phases. In each phase participants are presented with 43
50 images of food items. The food items represent an array of dietary options (Steinglass et al.,
51 2015). Twenty-five food items are low fat (<30% calories from fat) and 18 are high fat (>30%
52 calories from fat), as determined by Foerde et al. (2018). In the Health phase, participants
53 rate the healthiness of each food item on a 5-point scale (1 = "Unhealthy", 5 = "Healthy"). In
54 the Taste phase, participants rate the tastiness of each food item in a similar fashion, (1 =
55 "Bad", 5 = "Good"). In the Choice phase, in each trial participants choose between the
56 presented food item and a "Neutral" reference food item (rated as 3 in both Health and
57 Taste phases). If no item is rated 3 on both scales, an item rated 3 on Health and greater
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3 than 3 on the Taste scale is selected as a reference food. Good test-retest reliability of the
4 FCT suggests that it is suitable for measuring food-based decision-making in studies with
5 multiple assessment points (Foerde et al., 2018).
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9 (3) *State food craving - Food craving after cue exposure task*

10 The Food Challenge Task (FCT) (Kekic et al., 2017; Meule et al., 2018) will be used to
11 examine cue-induced food craving. In this task, participants rate their state food craving
12 using the Food Cravings Questionnaire State Version (Cepeda-Benito et al., 2000; Meule et
13 al., 2012) before and after being presented with a video on a computer screen of foods
14 shown to be highly appetising and to elevate hunger levels (Kekic et al., 2017). The
15 questionnaire consists of 15 items that measure the strength of food cravings (i.e. *I would*
16 *feel more alert if I could satisfy my craving*). Participants are asked to indicate how much
17 they agree with each statement 'at this very moment' using a five-point scale (from 1
18 'strongly disagree' to 5 'strongly agree'). There are five craving subscales; intense desire to
19 eat, anticipation of relief from negative states, physiological craving, preoccupation with
20 food or lack of control over eating and anticipation of positive reinforcement. Scores can be
21 calculated for specific subscales or a total score can be calculated (ranging from 15 to 75).
22 This questionnaires will be completed using Inquisit 5 (Millisecond Software), and the video
23 shown using QuickTime player.
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30 (4) *Trait food craving*

31 The Yale Food Addiction Scale Version 2.0 (YFAS 2.0; Gearhardt, Corbin, & Brownell, 2016) is
32 the most commonly used instrument to assess food-related addictive behaviours (Steward
33 et al., 2018). This self-report questionnaire consists of 35 items scored on an 8-point Likert
34 scale (from 0 = never to 7 = every day) and is adapted to assess addictive eating behaviours
35 based on DSM-5 substance-related and addictive disorders criteria (APA, 2013). It refers
36 specifically to consumption of foods high in fat, sugar, salt or refined carbohydrates. It
37 includes items that assess specific criteria, such as diminished control over consumption, a
38 persistent desire or repeated unsuccessful attempts to quit, withdrawal, and clinically
39 significant impairment (i.e. *'I kept eating in the same way even though my eating caused*
40 *emotional problems'*). The YFAS includes two scoring options: 1) a "symptom count" ranging
41 from 0 to 7 that reflects the number of addiction-like criteria endorsed and 2) a categorical
42 scoring option that classifies respondents as having either no, mild, moderate or severe
43 'food addiction'. The YFAS has received psychometric support in binge eating populations
44 (Gearhardt, White et al., 2013; Carter, Van Wijk & Rowsell, 2019), and obese bariatric
45 surgery patients (Clark & Saules, 2013; Meule, Heckel, & Kübler, 2012). The YFAS 2.0 was
46 developed to maintain consistency with the current diagnostic understanding of addiction
47 and to improve the psychometric properties of the original YFAS. Exceeding the food
48 addiction threshold was more strongly associated with obesity for the YFAS 2.0 than the
49 original YFAS. The YFAS 2.0 has demonstrated good internal consistency (Carter, Van Wijk &
50 Rowsell, 2019), as well as convergent, discriminant and incremental validity (Gearhardt,
51 Corbin & Brownell, 2016).
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59 (5) *Food intake in a Bogus Taste Test*

60 Actual food consumption will be measured by means of a Bogus Taste Test (Robinson et al.,

2017); a food consumption test presented under the guise of a taste test. Participants will be instructed to rate 3 bowls of highly palatable high-calorie food items (chocolate, sweets, crisps) in terms of their visual attractiveness, smell, and taste on a paper form. The researcher will inform the participant that she/he will leave the room for 10 minutes and during this time they can complete their ratings and are free to eat as much of the offered items as they like. A small bin with lid will be provided and participants will be instructed to consume as much food as they need or want, and to discard the remainder of the food items in the bin before 10 minutes are over. After the participant has left, the discarded food items will be recovered from the bin, sorted, and placed in their original bowls. Consumption will be determined by weighing the bowls both 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.

(6) *Delay discounting*

Delay Discounting Task with Money and Food (Odum, Baumann, & Rimington, 2006): 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 dollars worth) and money (10 dollars) or for relatively large maximum amounts of food (100 dollars worth) and money (100 dollars). Performance on this task can be used to study self-regulation, delayed gratification and valuation of reward. This task will be performed using Inquisit 5 (Millisecond Software).

(7) *Inhibitory control*

(i) *Go/No-Go task*: 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 food specific version of the cued go no-go task (Teslovich et al., 2014) measures impulsivity and response inhibition with respect to appetising food and nonfood items (i.e. toys), via assessing 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 set of stimuli consists of 30 colour images of common high- (8) and low-calorie (7) foods and common toys (15). The outcome variables include: (1) overall reaction time (RT) in milliseconds during correct “go” trials, (2) rate of omission errors (missed “go” trials), and (3) false alarm rate (rate at which participants erroneously press to a no-go stimulus). This task will be performed using Inquisit 5 (Millisecond Software).

(i) *Stop Signal Task (SST)*: This is a task measuring inhibitory control. Participants are required to engage in a computer task but withhold their response in the presence of a stop signal. This SST includes food-specific and neutral non-food stimuli in the same task (adaptation of Manasse et al., 2016). This allows for isolation of any unique food specific inhibitory control deficits from general difficulties inhibiting responses. The outcome measure is the stop signal reaction time (SSRT). The SSRT is calculated for each set of stimuli

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3 (i.e., SSRT stimulus type) for each subject by subtracting the average stop signal delay from
4 the average reaction time on “go” trials (Verbruggen & Logan, 2008). The recording
5 accuracy of reaction time and stop signal delay measurement is in milliseconds. A smaller
6 SSRT is indicative of greater inhibitory control and a larger SSRT reflects weaker/impaired
7 inhibitory control. This task will be performed using Inquisit 5 (Millisecond Software).
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10 (8) *Mood and emotion regulation*

11 The Emotion Regulation Questionnaire (ERQ) (Gross & John, 2003): A 10-item scale designed
12 to measure respondents’ tendency to regulate their emotions in two ways: (1) cognitive
13 reappraisal and (2) expressive suppression. Respondents answer each item on a 7-point
14 Likert-type scale ranging from 1 (strongly disagree) to 7 (strongly agree). This will be
15 administered at pre-assessment, post-assessment and follow-up.
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19 Positive and Negative Affect Schedule (PANAS) (Watson, Clarke & Tellegen, 1988): The
20 PANAS consists of two 10-item self-report scales which measure positive and negative
21 affect. On a Likert scale ranging from 0 (very slightly or not at all) to 4 (extremely),
22 participants rate the extent to which they have experienced each of the 20 descriptors
23 within a particular time frame (“right now” in the current study). Two scores are generated:
24 positive (PANAS-positive) and negative (PANAS- negative) affect. This will be administered
25 at pre-assessment, post-assessment and follow-up.
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29 Depression, Anxiety and Stress Scale (21-item version; DASS-21) (Lovibond & Lovibond,
30 1995): This is a 21 item self-report questionnaire which aims to evaluate mood, anxiety and
31 stress levels over the previous week. The DASS-21 will be administered at pre-assessment,
32 post-assessment and follow-up.
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35 (9) *Within session measures (immediately after each [ABM+real/sham tDCS] treatment 36 session)*

37 (i) Paper-based Visual Analogue Scales (VAS) assessing current hunger, feeling of fullness,
38 urge to eat, urge to binge eat, feeling low, level of tension, level of stress, level of anxiety.
39 These scales consist of a 10cm line. Participants are requested to indicate on this line a
40 degree or level of a specific emotion or behavioural urge. There are indications of what
41 range (e.g. from 'not at all' to 'extremely').
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44 (ii) Tolerance, discomfort and side effects: An evaluation of discomfort with the training
45 session (tDCS and ABM aspects separately) will be completed with another paper-based
46 10cm VAS (rated from none to extreme discomfort). Participants will be asked to report any
47 side effects in an open ended question.
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____1_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_____1_____
Funding	4	Sources and types of financial, material, and other support	_____12_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____12_____
	5b	Name and contact information for the trial sponsor	_____12_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____12_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____11_____

1 **Introduction**

2

3 Background and rationale 6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention _____ 2-4 _____

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6 6b Explanation for choice of comparators _____ 4 _____

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8 Objectives 7 Specific objectives or hypotheses _____ 4 _____

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10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) _____ 5 _____

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14 **Methods: Participants, interventions, and outcomes**

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16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained _____ 6 _____

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19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) _____ 5 _____

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22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered _____ 9-10 _____

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25 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) _____ 11 _____

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27 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) _____ 11 _____

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29 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial _____ 4, 11 _____

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32 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended _____ 6-9 _____

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1	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	___6__
2				
3				
4	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___5__
5				
6				
7	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___11__
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10 **Methods: Assignment of interventions (for controlled trials)**

11 Allocation:

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13				
14	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	___5-6__
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20	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___6__
21				
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24	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___5__
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27	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___5__
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31		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___6__
32				
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35 **Methods: Data collection, management, and analysis**

36				
37	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___6-8__
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1		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____10-11_____
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4	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____10-11_____
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8	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____10_____
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11		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____10_____
12				
13		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____10_____
14				
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17	Methods: Monitoring			
18				
19	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____10_____
20				
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25		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____11_____
26				
27				
28	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____11_____
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31	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____n/a_____
32				
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35	Ethics and dissemination			
36				
37	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____1, 13_____
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1	Protocol	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____ 1, 12_____
2	amendments			
3				
4				
5	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ 12_____
6				
7				
8		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ n/a_____
9				
10				
11	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____ 10-11_____
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14	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____ 12_____
15				
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18	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____ 10_____
19				
20				
21	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____ 11_____
22				
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25	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____ 1, 11_____
26				
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29		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ 12_____
30				
31		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ n/a_____
32				
33				
34	Appendices			
35				
36	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____ 24_____
37				
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39	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____ n/a_____
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1 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
2 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
3 [“Attribution-NonCommercial-NoDerivs 3.0 Unported”](#) license.
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For peer review only



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1 (no results)
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2-4
	2b	Specific objectives or hypotheses	4-5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9-10
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	5
	7b	When applicable, explanation of any interim analyses and stopping guidelines	11
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5-6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5-6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	n/a
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	n/a
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	n/a
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	n/a
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	n/a
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	n/a
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	n/a
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	n/a
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	12

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming; for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Combining cognitive bias modification training (CBM) and transcranial direct current stimulation (tDCS) to treat binge eating disorder: study protocol of a randomised controlled feasibility trial

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Combining cognitive bias modification training (CBM) and transcranial direct current stimulation (tDCS) to treat binge eating disorder: study protocol of a randomised controlled feasibility trial

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Key words: cognitive bias modification, transcranial direct current stimulation, eating disorders, binge eating, treatment

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ABSTRACT

Introduction: Binge Eating Disorder (BED) is a common mental disorder, closely associated with obesity. Existing treatments are only moderately effective with high relapse rates, necessitating novel interventions. This paper describes the rationale for, and protocol of, a feasibility randomised controlled trial (RCT), evaluating the combination of transcranial Direct Current Stimulation (tDCS) and a computerised cognitive training, namely Approach Bias Modification training (ABM), in patients with Binge Eating Disorder who are overweight or obese. The aim of this trial is to obtain information that will guide decision making and protocol development in relation to a future large-scale RCT of combined tDCS + ABM treatment in this group of patients, and also to assess the preliminary efficacy of this intervention. **Methods and analysis:** 66 participants with DSM-5 diagnosis of BED and a body mass index (BMI) of >25 kg/m² will be randomly allocated to one of 3 groups: ABM + real tDCS; ABM + sham tDCS or a waitlist control group. Participants in both intervention groups will receive 6 sessions of ABM + real/sham tDCS over 3 weeks; engaging in the ABM task while simultaneously receiving bilateral tDCS to the dorsolateral prefrontal cortex. ABM is based on an implicit learning paradigm in which participants are trained to enact an avoidance behaviour in response to visual food cues. Assessments will be conducted at baseline, post-treatment (3 weeks), and follow-up (7 weeks post-randomisation). Feasibility outcomes assess recruitment and retention rates, acceptability of random allocation, blinding success (allocation concealment), completion of treatment sessions and research assessments. Other outcomes include eating disorder psychopathology and related neurocognitive outcomes (i.e. delay of gratification and inhibitory control), BMI, other psychopathology (i.e. mood), approach bias towards food, and surrogate endpoints (i.e. food cue reactivity, trait food craving, and food intake).

Ethics and dissemination: This study has been approved by the North West - Liverpool East Research Ethics Committee. Results will be published in peer-reviewed journals.

Trial registration number: ISRCTN35717198

Strengths and limitations of this study

- The ICARUS study is the first randomised controlled feasibility trial of multi-session transcranial Direct Current Stimulation (tDCS) combined with Cognitive Bias Modification training (CBM) for adults with Binge Eating Disorder.
- ICARUS will compare [tDCS + CBM] vs. [sham tDCS + CBM] and a wait-list control group.
- ICARUS is designed to answer questions about the efficacy of the treatments tested.
- Results would need to be replicated in a larger trial before recommendations for tDCS + CBM as a treatment adjunct for patients receiving outpatient treatment for BED can be made.

INTRODUCTION

Binge Eating Disorder (BED) is the most prevalent eating disorder (ED) worldwide, with 1-3% of the general population meeting diagnostic criteria[1,2]. Binge eating is a core symptom, characterised by consumption of large amounts of food, a sense of loss of control, and significant distress. Nearly 80% of those with lifetime BED have a comorbid psychiatric disorder, such as mood, anxiety, substance use disorders or another ED[2]. Due to the lack of compensatory behaviours (e.g. vomiting, excessive exercising), BED is often accompanied by, or leads to, obesity and associated physical complications[3,4]. In the general population, approximately 30-42% of people with BED are obese[2,5,6]. Around 30% of treatment-seeking obese people[7–9] and up to 47% of bariatric surgery candidates have full or partial BED[1,10,11]. Whilst BED itself has considerable individual and societal costs[12], the combination of BED and obesity is associated with more severe obesity, greater medical and psychiatric comorbidity, greater functional impairment and perinatal complications[12–15]. Treatments for BED and obesity are sub-optimally effective, with cognitive behavioural therapy (CBT)[16] and some medications[17] reducing binge eating and related psychopathology[1], and approximately 50-60% of patients achieving abstinence from bingeing at the end of treatment[18] with some sustained cessation at follow-up[19]. However, drop-out rates in established BED treatments reach 12-34%, and 30%-50% of BED patients relapse in long-term follow-ups[20–22], indicating that a substantial proportion do not maintain binge eating remission. Lisdexamfetamine[23] and topiramate[24] also reduce weight in the short-term but have considerable side effects[25], and their longer term efficacy is uncertain. Thus, there is a need for novel treatment developments.

The aetiology of BED is widely seen as multi-factorial. Emerging neurobiological models emphasise both the role of stress in the onset and maintenance of the disorder[26,27], and the development of addiction-like features; craving, tolerance and binge escalation over time[28,29], impulsivity and compulsivity, alterations in executive function and attention[30] and reward-related decision making[31].

Upon encountering images of high-calorie food, BED patients report enhanced reward sensitivity and exhibit stronger medial orbitofrontal cortex responses compared to healthy controls and participants with bulimia nervosa[32]. In individuals with obesity, who may or may not have BED, activation in the ventral striatum (part of the reward system) has been found to be higher compared to normal-weight controls [33], in tandem with a more pronounced approach bias towards appetising food images [34,35], leading to greater likelihood of consumption. Furthermore, poor reward-related decision making behaviour may be a maintaining factor in obesity[36]. Converging data using different methodologies, such as brain imaging, eye tracking, and behavioural test paradigms [37] have found that patients with BED demonstrate a higher arousal rate in response to food stimuli, a concurrent motor plan to start eating, a higher reward sensitivity, and greater inhibitory deficits as compared to individuals without BED[32,38,39]. Those with obesity and BED (compared to obesity alone) have demonstrated that their attentional bias to food images held higher motivational value[40], and responded more to high calorie food images in sites of cognitive planning of motor movements, driven by emotions, which may reflect impulsive tendencies in the face of a binge-eating trigger. This tendency to approach and consume palatable food items may thus be compounded by a greater sensitivity to reward and a decreased capacity to inhibit action tendencies. This is corroborated by the recent finding that individuals with BED or Bulimia Nervosa

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3 (BN) show higher food cue reactivity (increased cravings) when exposed to visual food cues
4 compared to healthy controls [41]. Such accumulating evidence of BED as a unique diagnostic group
5 situates it as a distinct phenotype within the obesity spectrum that is characterised by increased
6 impulsivity [42].
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10 Conventional treatments of BED, such as CBT may not be best suited to target highly automatic
11 cognitive processes that occur at an early stage in information processing and that are considered to
12 contribute to food craving and associated maladaptive cognitions/behaviours. Two “brain-directed”
13 treatments may provide an avenue for modifying these processes: Approach Bias Modification
14 training (ABM) and transcranial Direct Current Stimulation (tDCS).
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17 Approach Bias Modification training (ABM) is a form of cognitive bias modification training (CBM)
18 that aims to retrain approach bias tendencies (reach out towards) into avoidance ones (move away
19 from)[43] regarding stimuli such as appetitive cues. Participants are systematically trained to show
20 an avoidance movement in response to illness-related rewarding stimuli (e.g. food or alcohol) on a
21 computer screen. ABM techniques have shown potential in several pilot and large-scale randomised
22 controlled studies to treat alcohol[44] and tobacco[45] addictions, and to reduce consumption of
23 cannabis[46] and unhealthy foods[47,48]. ABM has also yielded promising results in people with high
24 levels of food craving and in bulimic eating disorders, including BED[49,50]. However, mixed results
25 in empirical studies across these domains[51,52] raise methodological issues of ABM studies to date,
26 such as low statistical power and suboptimal choice (or absence) of control groups[53] and
27 administration of single versus multiple training sessions.
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31 Transcranial Direct Current Stimulation (tDCS) is a form of non-invasive brain stimulation (NIBS) that
32 has been used as a treatment adjunct for a range of psychiatric disorders, such as depression,
33 schizophrenia and addictions[54–56]. Preliminary evidence suggests that tDCS and other forms of
34 non-invasive brain stimulation are promising tools to reduce food craving, ED symptoms and body
35 weight in bulimic EDs, including BED, and obesity[57]. Additionally, some studies indicate that NIBS
36 may reduce depression/stress levels and improve reward-based decision making in ED patients[58].
37 A frequent stimulation target is the dorsolateral prefrontal cortex (dlPFC) which plays a major role in
38 cognitive-inhibition, emotion regulation, and reward processing[58–61]. Although precise
39 mechanisms of action of tDCS have yet to be understood, a key hypothesis in relation to BED is that
40 enhancing dlPFC activity via tDCS alters the reward-cognition balance towards facilitation of
41 cognitive control and suppression of reward-related mechanisms driving food
42 craving/overeating[62].
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49 If given concurrently (i.e. ‘online training’), NIBS is reported to boost the effects of cognitive training
50 on the reduction of cognitive biases and the improvement of response inhibition[63]. NIBS may
51 enhance synaptic strength in neuronal pathways activated by cognitive training, amplifying effects of
52 training, and thus cognitive bias modification efficacy [64]. As the effectiveness of tDCS may thus be
53 improved by pairing administration with a cognitive task inducing activity in the target brain
54 region[65–67], such combined treatment interventions have been investigated among alcohol
55 dependent inpatients (ABM and tDCS)[68], and to enhance inhibitory control related to food
56 consumption (Go/No-Go Task and tDCS)[65]. The insignificant findings from these studies warrant
57 commentary that to date, studies that have found positive effects of tDCS have either included
58 obese participants or have had multisession protocols[65,69–71]. As this study incorporates both
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aspects, it is optimally designed to yield significant results.

In light of both the individual and societal burden incurred by the rising prevalence of BED and obesity, research interventions informing treatments that lead to stable and long-lasting remission are of critical importance, and novel therapies may play a role in serving as adjuncts to treatment as usual, to enhance improvement in clinical outcomes obtained from engaging with eating disorder treatment services. This research trial is the first to combine two promising novel intervention strategies in an integrated treatment and will yield important findings to shape future clinical trials. The intervention conditions of this feasibility study will involve 6 sessions of concurrent ABM and real or sham tDCS over 3 weeks, and will assess participant acceptability and dropout rates at this treatment frequency and duration. Additionally, the frequency of participants' ED symptoms and other outcomes related to general psychopathology and neurocognition will be measured before and after the study interventions to assess treatment success. In summary, this proof-of-concept and feasibility study will establish the utility of concurrent ABM + real tDCS in improving clinical outcomes in participants with BED, compared to ABM + sham tDCS, and a wait-list control group.

STUDY AIMS

In line with established recommendations for outcomes of feasibility trials[72], which at present are supported by the National Institute for Health Research, the primary aim is to assess the feasibility of using concurrent ABM + real tDCS compared to concurrent ABM + sham tDCS as a potential adjunct to treatment as usual (TAU) in this patient population, and acquire key information to inform the development of a large-scale randomised sham-controlled trial (RCT).

The specific objectives of the proposed feasibility study are to:

1. Establish the feasibility of conducting a large-scale RCT of ABM + tDCS in patients with BED by assessing recruitment, attendance, and retention rates;
2. Determine the practicality of administering both ABM and tDCS simultaneously;
3. Determine the best instruments for measuring outcomes in a full trial by examining the quality, completeness, and variability in the data;
4. Estimate the treatment effect sizes and standard deviations for outcome measures to inform the sample size calculation for a large-scale RCT;
5. Evaluate whether the treatment is operating as it is designed by analysing process measures, such as within-session visual analogue scales (VAS) of key ED symptoms;
6. Determine whether patients with BED evaluate concurrent ABM + tDCS as acceptable and credible;
7. Obtain information about patients' willingness to undergo random allocation to ABM paired with either real or sham tDCS administration, or the wait-list control condition.

A secondary aim is to investigate the potential efficacy of concurrent delivery of both forms of treatment on binge eating disorder.

This will involve evaluating if:

1. Concurrent sessions of ABM + real tDCS are superior to ABM + sham tDCS and to wait-list control in terms of frequency of objective binge eating episodes, food cue reactivity, food craving, food intake, eating disorder psychopathology and mood.

2. Concurrent ABM + tDCS is superior to the two other conditions in having an effect on the targeted neurocognitive mechanism (approach bias for high calorie food) and related neurocognitive parameters (i.e. impulsivity, delayed gratification, emotional regulation).
3. Concurrent ABM and sham tDCS is superior to the waitlist control in eliciting therapeutic effects on the aforementioned clinical outcomes and neurocognitive mechanisms, yet demonstrates an efficacy level below that of concurrent ABM and real tDCS.

METHODS AND ANALYSIS

This study protocol has been written according to the SPIRIT statement (Standard Protocol Items for Randomised Trials)[73] and the CONSORT 2010 statement (Consolidated Standards of Reporting Trials)[72].

Study design

The ICARUS trial (Investigating Concurrent Approach Bias Modification Training and Transcranial Direct Current Stimulation in Binge Eating Disorder) is an exploratory randomised controlled feasibility trial with three parallel treatment conditions; ABM + real tDCS, ABM + sham tDCS and wait-list control. All participants across the two intervention groups will receive a treatment protocol of 6 sessions of ABM + real/sham tDCS conducted over 3 weeks. The comparator groups of a wait-list control and ABM + sham tDCS are necessary to evaluate the potential effect of real versus sham tDCS in participants with BED. The wait-list control group will be examined at the same time points to control for the possibility that improvements in the intervention groups are simply due to regression to the mean, spontaneous remission or other non-specific time effects. Any participants who are engaging in treatment for their ED will continue with TAU, and thus this selection of comparators is deemed acceptable. Within treatment session measures will involve visual analogues scales evaluating mood, stress and eating disorder symptoms. Assessments will be conducted 3 times during the study; at baseline, post-treatment (week 3), and at follow-up (week 7).

Participants

Inclusion criteria entail: (1) male and female community-dwelling adults (aged 18-70); (2) overweight or obese according to WHO criteria (BMI>25 kg/m²)[74]; (3) a diagnosis of full-syndrome or sub-threshold Binge Eating Disorder according to the DSM-5[75]; (4) fluency in English; (5) normal or corrected to normal vision .

Exclusion criteria entail: (1) all known contraindications to tDCS[76]; (2) pregnancy; (3) a current significant/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) taking psychotropic medication other than a stable dosage of selective serotonin reuptake inhibitors (SSRI) for at least 14 days prior to study enrolment; (6) allergies to any of the foods presented in the study; (7) smoking >10 cigarettes per day; (8) drinking >3-4 units (men) or 2-3 units (women) of alcohol per day. In line with the CONSORT guidelines[77,78], we will record the number and reasons for any participants we must exclude, or any who decline consent or withdraw from the study.

Sample size

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3 As ICARUS is a feasibility study, an a priori sample size calculation is not necessary. Rather, its aim is
4 to provide effect sizes on which future large-scale studies can be powered. Total study sample sizes
5 of n=24 to n=50 have been recommended for feasibility trials with a primary outcome measured on
6 a continuous scale, mainly because estimates of the standard deviation for normally distributed
7 variables tend to stabilise around this size[79,80]. We have chosen a target end study sample size of
8 n=60, (i.e. exceeds the upper end recommended for feasibility trials). However, assuming the
9 attrition to follow-up rate is a = 0.10 (as found in previous eating disorder trials [81,82]) and applying
10 an attrition correction factor of $1/(1-a)$, we will recruit an actual sample size of 66, i.e., 22
11 participants per group.
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15 16 **Randomisation**

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18 After the baseline assessment, participants will be allocated to one of three conditions at random to
19 receive 6 sessions of either concurrent ABM + real tDCS or ABM + sham tDCS, or no intervention in
20 the wait-list control condition. As a proportion of participants recruited from an outpatient eating
21 disorder clinic will be on a waiting list to receive treatment at the time of enrolment in this study and
22 may commence treatment shortly after study enrolment, this study will not seek to balance groups
23 in terms of therapy engagement or medication usage. Participants in the wait-list control group will
24 be offered the opportunity to receive ABM + real tDCS after the end of the follow-up. Participants
25 will be individually randomised on a 1:1:1 ratio to the intervention or control groups in equal
26 numbers. The generation and implementation of the randomisation sequence will be conducted
27 independently from the trial team through a randomisation administrator who is not involved in any
28 recruitment or research activity related to the ICARUS study. Online randomisation software (Sealed
29 Envelope, London, UK) will be used for this purpose. Upon participant enrolment, the researcher will
30 contact the randomisation administrator, who will inform this researcher in charge of carrying out
31 the intervention of the participant's allocation via phone or email.
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36 37 **Blinding**

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39 Double blinding is implemented only for the intervention group cohorts of the trial. The research
40 assessor will remain blind to each participant's tDCS assignment within the two intervention
41 conditions until after the participant has completed the follow-up assessment. This double blinding
42 protocol will be ensured via administration of the tDCS (NeuroConn DC-STIMULATOR PLUS) using
43 "study mode". This involves a five-digit numerical code unique to each patient will be inputted into
44 the device prior to the participant's testing session, that will initialise either sham or real (active)
45 stimulation. The tDCS administrator and participants will remain blind to tDCS stimulation type
46 throughout the study. Set-up of the randomisation codes and programming of the tDCS device will
47 be performed by an investigator not involved in the trial. To assess blinding success, each participant
48 and the researcher will be asked to guess the treatment allocation at the end of the 6 treatment
49 sessions and to indicate how certain they are of this guess. The study group allocation will be
50 revealed to the participant after their follow-up assessment. In the event of a reported change in a
51 participant's medication, or a new clinical diagnosis made during their study participation, the early
52 unblinding of study condition for an intervention group participant will be permissible. The trial
53 database will be maintained 'blind' until the point of study data analyses.
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Recruitment

The study will take place at the Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London (KCL), UK. Participants will be recruited from the Eating Disorders Service at the South London and Maudsley NHS Foundation Trust, from the KCL research recruitment webpage and social media account, and via posters placed on notice boards on KCL campuses. Participants who have previously taken part in research at the KCL Eating Disorders Unit and who have consented to be informed of future studies may also be contacted. The ICARUS study will also be advertised on the Beat (National Eating Disorders Association) website, callforparticipants.com and www.mqmentalhealth.org. Potential participants will receive written and verbal study information and will be screened for eligibility. Eligible participants will provide informed written consent for study participation as a prerequisite for enrolment (See Appendices A and B).

Procedure

Figure 1 illustrates the timeline of the study procedures. All participants will partake in assessments at each of the three measurement points; baseline, post-treatment, and follow-up. Each assessment will comprise of an in-person study visit with tasks and measures, and online/hardcopy questionnaires and scales to be completed at home by the participant within 36 hours following the study visit. Table 1 details the tasks and measures allocated to each assessment and training visit. After the baseline assessment, participants are randomised to one of 3 groups; (1) ABM + real tDCS, (2) ABM + sham tDCS, or a waitlist control group (CG). Participants allocated to an intervention group will be offered 6 sessions of ABM + real/sham tDCS across 3 weeks. All study participants may receive TAU e.g. if they are currently engaged in outpatient treatment for their ED. The control group will not receive any study intervention, and any participants receiving outpatient services treatment for their ED will continue TAU during this 3 week period. The post-treatment assessment will be conducted on all participants after the 6th (final) session of ABM + real/sham tDCS for the intervention groups, and 3 weeks after the baseline assessment for the control group. The follow-up assessment will be conducted 28 days after the end of treatment, i.e. 7 weeks post-randomisation. A follow-up period is included because, if the effects of the intervention result from increased neuroplasticity, behavioural changes may need time to emerge. Assessing the longevity of favourable clinical outcomes beyond the treatment period is also relevant to the objectives of this feasibility study. The researcher conducting the assessment and testing sessions will remain blind to the study condition of intervention group participants until the follow-up has been completed.

Outcome assessment

Measures of feasibility, safety and adherence will be collected throughout the study. Outcomes related to ED symptoms, general psychopathology and neurocognition will be measured before and after the study intervention to assess treatment success. Each assessment session will be split into an in-person visit and at-home component to accommodate time constraints and minimise disruption to task performance due to participant fatigue. The in-person assessment measures will take approximately 75 minutes to complete, and the online questionnaires will take approximately 45 minutes.

Outcome Measures

Feasibility outcomes

As this is a feasibility study, an extensive range of outcome measures are included to help determine which are most sensitive to detecting a treatment effect. This will enable us to determine primary outcome(s) for a future large-scale RCT. However, based on previous research[49], the Eating Disorder Examination Questionnaire (EDE-Q) is anticipated to be a key outcome measure.

Intervention/service related outcomes

Feasibility outcomes include recruitment, attendance and retention rates, and acceptability of treatment by participants. Patients' acceptance of study interventions will be assessed by measuring treatment dropout rates and via the treatment tolerance and acceptability questionnaires. An interview assessment of treatment experience will be conducted with 20 participants after the follow-up is completed. 10 participants from each intervention group will be invited to provide feedback on their initial expectations and experiences of the ABM + real/sham tDCS treatments, perceived strengths and weaknesses of the treatment they received, and suggestions for improvements in procedures. Interviews will be recorded, transcribed and analysed using thematic analysis. This will allow future studies to consider patients' feedback in the development of research and clinical protocols of concurrent ABM and tDCS.

Clinical outcomes

Eating disorder and related psychopathology

(a) Eating Disorder Examination (EDE-Q)[83]: The EDE-Q is a widely used measure of eating-disordered behaviour and is widely regarded as the instrument of choice for the assessment of EDs. This will be administered at baseline, post-assessment and follow-up.

b) Body Mass Index (BMI (kg/m²)): This assessment of body composition provides accurate estimates of body fat percentages in adults, where sex and age are factored into the analysis measuring height and weight[84]. To calculate BMI, height and weight measurements will be obtained by the researcher at baseline, post-assessment and follow-up.

(c) Approach bias assessment tasks

To identify the most sensitive method of assessing change in approach bias towards high-calorie food items, two different computerised measures of approach bias will be used. In the Food Approach-Avoidance Task (F-AAT)[85] participants are shown colour photographs of high-calorie, palatable foods such as chocolate, cake, and pizza, and non-food household and office items such as sponges and stationary on a computer-screen[86]. They are instructed to approach and avoid these stimuli by moving a joystick toward themselves (approach) or away from themselves (avoidance). In the Stimulus Response Compatibility Task (SRC)[87], participants perform a symbolic movement by making a manikin image walk toward (approach) or away from stimuli (avoidance). See Appendix C for more detailed information. Both of these tasks will be administered at baseline, post-assessment and follow-up.

(d) Food choice attitudes/behaviour

The Food Choice Task[88–90] is a computer-based paradigm that measures responses to images of

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3 foods to assess food attitudes and characteristics of eating behaviour. Participants rate images of
4 food on a computer screen according to healthiness as well as tastiness. Based on these ratings they
5 are then offered a choice between a food that they consider “neutral” and a series of other foods.
6 See Appendix C for more detailed information. This task will be performed at baseline and post-
7 assessment.
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11 *(e) Food craving after cue exposure task*

12 The Food Challenge Task (FCT)[41] will be used to examine cue-induced food craving. In this task,
13 participants rate their state food craving using the Food Cravings Questionnaire State Version[91,92]
14 before and after being presented with a video on a computer screen of foods shown to be highly
15 appetising[93]. See Appendix C for more detailed information. This task will be performed at
16 baseline and post-assessment.
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20 *(f) Trait food craving*

21 Three questionnaires will be used to comprehensively assess mechanisms implicated in trait food
22 craving. The Food Cravings Questionnaire Trait Version - reduced (FCQ-T-r)[94] is a 15 items only
23 reduced version of a self-report questionnaire that measures trait levels of craving for food. The 21-
24 item Power of Food Scale (PFS)[95] scale assesses the psychological influence of the mere presence
25 or availability of food. It measures appetite for, rather than consumption of, palatable foods, at
26 three levels of food proximity (food available, food present, and food tasted). The Yale Food
27 Addiction Scale Version 2.0 (YFAS 2.0)[96] reflects the current diagnostic understanding of addiction
28 to further investigate the potential role of an addictive process in problematic eating
29 behaviour[75,97–101]. See Appendix C for more detailed information. Each of these scales will be
30 administered at baseline, post-assessment and follow-up.
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35 *(g) Food intake in a bogus taste test*

36 During the bogus taste test[102], participants will be instructed to rate and optionally consume
37 highly palatable high-calorie food items presented in 3 bowls. See Appendix C for more detailed
38 information. This task will be performed at baseline and post-assessment.
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42 *(h) Increased preference for delayed rewards*

43 The Delay Discounting Task with Money and Food[103] examines whether small amounts of food
44 would be discounted more steeply than money, as occurs with larger amounts. See Appendix C for
45 more detailed information. This will be administered at baseline, post-assessment and follow-up.
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49 *(i) Inhibitory control*

50 The cued Go/No-Go computer task is a classic test of executive function, requiring effortful response
51 inhibition, and measures impulse control by the ability to inhibit instigated, prepotent responses. A
52 food specific go/no-go task[104] measures impulsivity and response inhibition with respect to food
53 and nonfood items. The Stop Signal Task (SST)[105] measures inhibitory control. Participants are
54 required to engage in a computer task but withhold their response in the presence of a stop signal.
55 An adaptation of the food version of the SST[106] will facilitate a comparison of responses between
56 food and non-food categories. See Appendix C for more detailed information. Both of these tasks
57 will be performed at baseline, post-assessment and follow-up.
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Mood and emotion regulation

The Emotion Regulation Questionnaire (ERQ)[107] is designed to measure respondents' tendency to regulate their emotions regarding cognitive reappraisal and expressive suppression. The Positive and Negative Affect Schedule (PANAS)[108] measures the degree of positive or negative affect experienced "right now" in the current study. The Depression, Anxiety and Stress Scale (DASS-21)[109] evaluates mood, anxiety and stress levels over the previous week. See Appendix C for more detailed information. All of these measures will be administered at baseline, post-assessment and follow-up.

Within session measures

Within each training session, i.e. immediately before and after the ABM + real/sham tDCS procedure the researcher will administer paper-based Visual Analogue Scales (VAS) assessing current hunger, feeling of fullness, urge to eat, urge to binge eat, feeling low, level of tension, level of stress, level of anxiety, and any discomfort due to tDCS and ABM in the training session. See Appendix C for more detailed information.

Intervention

In both intervention groups participants will receive six sessions of concurrent ABM and real or sham tDCS which will be delivered twice a week for three weeks. A researcher trained in tDCS administration will deliver the training sessions.

Rationale for number of sessions:

Treatment parameters for interventions of ABM and tDCS separately in psychiatric disorder research have not yet been standardised and vary from 1-12 sessions across a timeframe of days to multiple weeks. Mixed results regarding optimal frequency of ABM sessions and related forms of cognitive bias modification has been reported[110]. A maximum accumulative effect of modification efficacy at 6 sessions has been found for approach bias modification for alcohol dependence[44]. While there is a similar paucity of specifications for treatment parameters within tDCS, multisession NIBS interventions are significantly more effective at reducing cravings and strengthening the ability to refrain from food consumption than single session protocols in eating disorders and obesity[111]. As a single session of tDCS on patients with BED was found to reduce craving and caloric intake[59], it was hypothesised that repeated administration of tDCS would enhance this effect and may decrease binge eating frequency.

Within session safety procedures

The participant's blood pressure and heartrate will be taken by the researcher immediately before and after the session. While the participant is comfortably seated, the tDCS and ABM will be administered at the same time, i.e. participants will engage in ABM training whilst receiving tDCS. Each session will last 20 minutes. The ABM training will start 5 minutes after the start of the brain stimulation. ABM training will take place over 10 minutes and tDCS will then continue for a further 5 minutes. Participants will be reminded that they have the option to withdraw immediately and terminate their participation in the study if they experience discomfort during tDCS administration, or if they wish to withdraw for any reason that they may or may not wish to disclose.

Approach bias modification training

The ABM programme will use an implicit learning paradigm, based on a modified version of the Food Approach/Avoidance Task (AAT)[85,112–114]. In this task, participants are shown pictures of food and control (i.e. neutral office) items. They are required to pull (pictures grow bigger) or push (pictures grow smaller) a joystick in response to the outer frame of the picture (round vs. rectangular), irrespective of the picture content. The training version of the Food-AAT utilises an implicit learning paradigm by presenting all food pictures in the “push” (i.e. avoid) format. The study procedure for ABM administration is aligned with previous research[50,115].

Transcranial direct current stimulation

TDCS (both real and sham) will be delivered using a NeuroConn® DC-STIMULATOR PLUS device at a constant current of 2 mA (with a 10-second fade in/out) using two 25cm² surface sponge electrodes soaked in a sterile saline solution (0.9% sodium chloride). The anode will be placed over the right dorsolateral prefrontal cortex (dlPFC) and the cathode over the left dlPFC. This montage has been used in sham-controlled studies on food craving, bulimia nervosa and BED[59]. The stimulation site will be located using the Beam F3 calculation method, which is based on the International 10-20 system. TDCS can occasionally result in mild discomfort during administration (i.e., tingling or itching sensation, a slightly metallic taste, occasional redness at the site of the electrodes). Fatigue, headache, nausea and insomnia have been reported as potential adverse reactions[116]. Participants who are at-risk for adverse effects[76] will be excluded from the study at the screening stage.

Data analysis

Data will be analysed with the Statistical Package of Social Sciences (SPSS). Feasibility outcome data will be analysed with appropriate summary statistics. To determine quality, completeness, and variability of the clinical outcome data, descriptive statistical analyses and graphical methods will be used. Intent-to-treat analyses will be performed. The size of the treatment effect on each outcome measure will be the difference in outcome data between those in the two treatment conditions and control condition at post-assessment and follow-up. Group differences will be estimated using linear mixed effects regression models, controlling for the baseline level of the outcome. The goal here is not to determine significant group differences but to establish a suitably precise effect size for the primary outcome at the post treatment assessment. This estimate will be used to guide the sample size of a future efficacy trial. Correlational analyses may be computed to analyse relationships between outcome variables and influences of potential covariates such as demographic variables, i.e. gender, age, BMI and clinical variables, i.e. start/stopping of psychotherapy, psychotropic medication and presence of comorbidities. Outcome data already obtained for participants who discontinue or deviate from the intervention protocol will be kept and analysed.

PATIENT AND PUBLIC INVOLVEMENT

Patients and/or public were not involved in the study design process, however we will obtain 20 intervention participants' qualitative views on their treatment experience in this study to inform future clinical trials.

ETHICS AND DISSEMINATION

Data management and data monitoring

Participant data will be anonymised and all anonymised data will be stored electronically on a password protected computer at the IoPPN. All trial data will be stored in line with the General Data Protection Regulation (GDPR) 2018. Hard copies of participant-related data (i.e. GP letters) will be kept in locked cabinets at the IoPPN, King's College London. The final trial data set will not be accessed by anyone other than members of the research team.

Data will be stored on manual files, 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 files will be securely locked in a lockable filing cabinet, and all electronic files will be password protected. Identifying information will be removed from the data, stored separately and replaced with a numeric identification code. 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 accessible to key researchers involved in the study.

The online component of the assessment will use Online Surveys software (formerly BOS). King's College London uses this software for large scale surveys, and it is fully compliant with UK data protection laws. Participants will be emailed the link after the in-person component of each assessment session, and instructed to complete the second online component of the assessment within 36 hours. Participants will also have the option to receive and complete a hard copy version of the questionnaires with a stamped addressed envelope to post back to the study researcher at the IoPPN.

It is intended that the results of this feasibility study will be reported and disseminated at national and international conferences. Research findings may also be disseminated through internal newsletters and publications in collaboration with Beat, the UK's largest eating disorder charity.

Owing to the size and nature of this small-scale feasibility study, a data monitoring committee was not deemed to be required. There are no scheduled interim analyses and this trial may be prematurely discontinued by the Chief Investigator on the basis of new safety information.

Ethics and safety aspects

This study has been approved by the North West - Liverpool East Research Ethics Committee. 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 and 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 ICARUS trial is registered with the International Standard Randomised Controlled Trial Number registry (number ISRCTN35717198). All participants will be asked by the study researcher to provide written informed consent prior to enrolment. Participants who are at-risk for adverse side effects^[76] will be excluded from the study at the screening stage (i.e. such as those with pregnancy or epilepsy). Current safety parameters of tDCS administration regarding voltage amplitude and duration of brain stimulation sessions will be adhered to. Participants have the option to withdraw immediately and terminate their participation in the study if they experience discomfort during tDCS administration, or if they wish to terminate

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3 their participation for any other reason that they may or may not wish to disclose. After each
4 training session, participants will complete the tolerance, discomfort and side effects questionnaire
5 to report any adverse effects of the intervention training session. The researcher will record this
6 description of any reported adverse effects, and record the severity and duration of symptoms and
7 how the adverse effect was managed at the following training session. If a participant reports a new
8 clinical diagnosis or change in medication during their involvement in the study, a decision regarding
9 their continued participation in the study will be made by the research team and withdrawal of the
10 participant may be deemed necessary. Standard King's College London insurance and NHS indemnity
11 arrangements apply to this study. To promote study adherence, upon completion of the follow-up
12 assessment, each participant will be reimbursed for their time, efforts and travel (£60 for
13 assessments and up to £60 for travel expenses). Additionally, participants in the wait-list control
14 group will be offered the opportunity to receive 6 sessions of ABM + tDCS after the follow-up.
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21 **DISCUSSION**

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23 The ICARUS study represents the first feasibility study that aims to exploit a synergistic therapeutic
24 effect by combining two brain-directed interventions in a single treatment intervention for BED. The
25 rising clinical need of individuals with BED is currently met with few available psychological and
26 neuropharmacological treatment options[117]. Therefore, such research advancing the
27 identification and validation of novel therapies is greatly warranted.
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31 This paper delineates the protocol for a feasibility trial which will inform future studies (i.e., provide
32 effect sizes for a large RCT) and contribute to the extant research advocating brain-directed
33 interventions for BED. The protocol aligns with current parameters of tDCS administration used to
34 treat BED and BN[58,59] and utilises a multitudes of measures to identify the most appropriate and
35 sensitive tools to detect treatment induced changes across pathological and neurocognitive
36 domains.
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40 Pragmatic concerns related to the recruitment process entail ensuring a sufficient and consistent
41 rate of participant enrollment to meet the target sample number within the allocated timeframe.
42 Additionally, drop-out rates for CBT treatment among a BED cohort are moderately high (17–
43 30%)[118], thus study adherence will need to be monitored, with a revision of incentives/
44 reimbursement if necessary. Participants who were randomly allocated to the wait list control may
45 avail themselves of 6 sessions of ABM + real tDCS after they have completed the study, which may
46 promote recruitment and participant retention. Documenting the management of these issues will
47 help to inform the development of a future large-scale RCT of this combined treatment adjunct for
48 BED.
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53 To conclude, investigating novel treatments for BED is an imperative issue. Combining ABM with
54 tDCS is the strategic amalgamation of two techniques that have already demonstrated therapeutic
55 efficacy in their own right. This feasibility RCT will be the first to systematically assess the
56 acceptability and efficacy of a noninvasive, safe and potentially effective treatment adjunct to other
57 therapies, which will enhance the ability of healthcare services to provide optimal care to patients
58 with BED.
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Trial progress

Recruitment will commence in February 2018 and data collection is expected to be complete (including follow-up assessments) by April 2020. Any substantial protocol amendments will be communicated to investigators via email and to other parties as required. Amendments to the study protocol will be reported in publications reporting the study outcomes.

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Authorship policy No professional writers were involved in this study protocol, nor will be involved in the study report write-up.

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Disclaimer The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests None declared

Patient consent Informed consent will be obtained by the researcher.

Ethics approval Ethical approval was given by the North West - Liverpool East Research Ethics Committee (ref: 18/NW/0648).

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Data sharing statement Not applicable

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Figure 1 Study procedure. The 3 assessment time points are baseline, post-assessment and follow-up. IG1 is intervention group 1; IG2 is intervention group 2, CG is the wait list control group.

Table 1 Study schedule of measurement and testing time points

	Screening of potential participants	Baseline assessment (all participants)	Training: 6 sessions of ABM + real tDCS	Training: 6 sessions of ABM + sham tDCS	Post-assessment (all participants)	Follow-up (all participants)
Approximate time since baseline	-----	-----	0-3 weeks	0-3 weeks	3 weeks	7 weeks
Informed consent		X				
EDDS, SCID-I	X					
TDCS safety screening	X					
Demographic information		X				
EDE-Q[83]		X			X	X
Inhibitory control tasks; Go/No-Go task[104], SST[106]		X			X	X
Delay Discounting Task with Money and Food[103]		X			X	X
Food related tasks; Food Choice Task[88], FCT, Bogus Taste Test[102]		X			X	
Approach bias assessment tasks; F-AAT[85], SRC[87]		X			X	X
Questionnaires & scales (incl. at home); EDRSQ[119], FCQ-T-r[94], PFS[95], YFAS 2.0[96], ERQ[107], PANAS[108], BIS-11[120], CIA[121], DGI[122], DASS-21[109]		X			X	X
Pre-[tDCS + ABM] measures: -Multiple VAS, blood pressure, pulse			X	X		

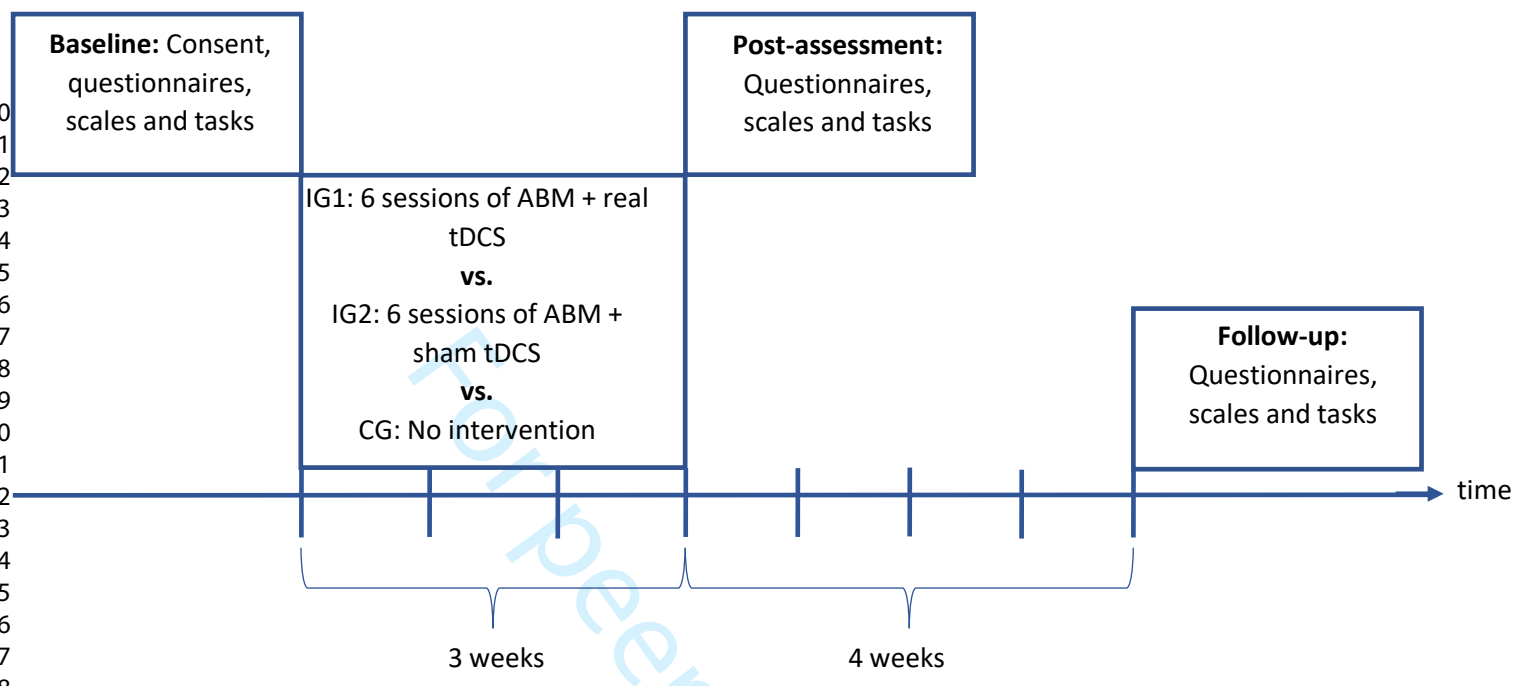
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Real or sham tDCS to dLPFC	X	X	
Approach Bias Modification training	X	X	
Post-[tDCS + ABM] measures:	X	X	
-Multiple VAS, blood pressure, pulse			
Tolerance, discomfort and side effects	X	X	
Acceptability questionnaire			X
Blinding assessment questionnaire			X

BIS-11; Barrett Impulsiveness Scale, CIA; Clinical Impairment Assessment, DASS-21; Depression, Anxiety and Stress Scale, DGI; Delayed Gratification Inventory, EDDS; Eating Disorder Diagnostic Screen, EDE-Q; Eating Disorder Examination, EDRSQ; Eating Disorder Recovery Self Efficacy Questionnaire, ERQ; Emotion Regulation Questionnaire, FCQ-T-r; Food Cravings Questionnaire Trait Version – reduced, PANAS; Positive and Negative Affect Schedule, PFS; The 21-item Power of Food Scale, SCID-I; Structured Clinical Interview for Diagnostic and Statistical Manual (DSM) Axis I Disorders, SRC; Stimulus Response Compatibility Task, SST; Stop Signal Task, YFAS 2.0; The Yale Food Addiction Scale Version 2.0, .

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Supplementary File

Appendix A: ICARUS study task, questionnaire, measure and scale information

(1) *Approach bias assessment tasks*

(i) Food Approach-Avoidance Task (F-AAT) (Rinck & Becker, 2007): The F-AAT is a computerised task that measures approach and avoidance behaviour by means of joystick movements in response to food and neutral stimuli presented on a computer screen. This task will be used to assess approach bias towards visual cues of high-calorie food (expected target cognitive mechanism of intervention). Images of palatable edible foods (i.e. chocolate, pizza) and non-edible objects (i.e. sponges, stapler) are used as in previously (Brockmeyer et al., 2019). The assessment version of the AAT is identical to the treatment version except that the required response is unrelated to the picture content (i.e. food and neutral stimuli are presented equally often in round and rectangular, i.e. push and pull, format). Format movement assignments are counterbalanced among participants (i.e., half push round pictures and half push rectangular pictures). When the joystick is pulled, the picture grows bigger, and diminishes in size when the joystick is pushed. Zooming-in and zooming-out via joystick movements enacts motions of approaching and avoiding respectively and thus combines the proprioceptive (arm movement) and exteroceptive (zooming feature) cues of approach and avoidance behaviour (Neumann & Strack, 2000; Brockmeyer et al., 2019). The assessment version of the AAT consists of 80 trials (40 food item pictures and 40 non-food item pictures). To evaluate approach bias towards food, a compatibility score is calculated by subtracting the median reaction times (RTs) of compatible trials (i.e., RT pull food + RT push nonfood) from median RTs of incompatible trials (i.e., RT push food + RT pull nonfood) (Brockmeyer et al., 2019; Becker et al., 2016; Vrijssen et al., 2018). A positive value indicates a food-specific approach bias (i.e. the participant is faster at pulling than pushing food pictures, relative to the approach bias towards non-food), whereas a negative value indicates an avoidance bias. This task will be performed using Inquisit 5 (Millisecond Software).

(ii) The Stimulus Response Compatibility Task (SRC) (De Houwer, Crombez, Baeyens, & Hermans, 2001): In this task, participants respond to images on a computer screen by pressing keys on the keyboard. Pictures are presented in the centre of the screen with a manikin (12 mm high) positioned 33 mm above or below the picture. Participants are required to categorise the presented pictures by making an approach response (pressing the *up* or *down* key to move the manikin toward the picture) or an avoidance response (pressing the *up* or *down* key to move the manikin away from the picture). After making a correct response, an animation is shown of the manikin walking toward the picture (approach) or away from the picture (avoidance) for 1,000 ms. After making an incorrect response, a red cross appears on the screen for 500 ms, after which the next trial starts. Fourteen food and fourteen non-food pictures will be used from the food-pics database (Blechert, Meule, Busch & Ohla, 2014). The experiment comprises 8 practice trials and 56 experimental trials. Bias scores will be calculated by subtracting the mean of approach food/avoid non-food trials from the mean of avoid food/approach non-food trials. A positive score indicates a food-related approach bias, with higher scores indicative of stronger biases. This task will be performed using Inquisit 5 (Millisecond Software).

(2) Food Choice Task

The Food Choice Task (Hare, Camerer & Rangel., 2009) adapted for eating disorders (Steinglass et al., 2015) is a computer-based paradigm that measures responses to images of foods to assess food attitudes and characteristics of eating behaviour. Food stimuli is used to investigate how individuals make decisions about what to eat, and measures decision-making around food by directly probing personal preferences. There are no learning requirements and individualised assessments of food along two dimensions (healthiness and tastiness) allow the tasks to be used in diverse populations with differing valuations of food. The task consists of three phases. In each phase participants are presented with 43 images of food items. The food items represent an array of dietary options (Steinglass et al., 2015). Twenty-five food items are low fat (<30% calories from fat) and 18 are high fat (>30% calories from fat), as determined by Foerde et al. (2018). In the Health phase, participants rate the healthiness of each food item on a 5-point scale (1 = "Unhealthy", 5 = "Healthy"). In the Taste phase, participants rate the tastiness of each food item in a similar fashion, (1 = "Bad", 5 = "Good"). In the Choice phase, in each trial participants choose between the presented food item and a "Neutral" reference food item (rated as 3 in both Health and Taste phases). If no item is rated 3 on both scales, an item rated 3 on Health and greater than 3 on the Taste scale is selected as a reference food. Good test-retest reliability of the FCT suggests that it is suitable for measuring food-based decision-making in studies with multiple assessment points (Foerde et al., 2018).

(3) State food craving - Food craving after cue exposure task

The Food Challenge Task (FCT) (Kekic et al., 2017; Meule et al., 2018) 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 (Cepeda-Benito et al., 2000; Meule et al., 2012) before and after being presented with a video on a computer screen of foods shown to be highly appetising and to elevate hunger levels (Kekic et al., 2017). The questionnaire consists of 15 items that measure the strength of food cravings (i.e. *I would feel more alert if I could satisfy my craving*). Participants are asked to indicate how much they agree with each statement 'at this very moment' using a five-point scale (from 1 'strongly disagree' to 5 'strongly agree'). There are five craving subscales; intense desire to eat, anticipation of relief from negative states, physiological craving, preoccupation with food or lack of control over eating and anticipation of positive reinforcement. Scores can be calculated for specific subscales or a total score can be calculated (ranging from 15 to 75). This questionnaires will be completed using Inquisit 5 (Millisecond Software), and the video shown using QuickTime player.

(4) Trait food craving

The Yale Food Addiction Scale Version 2.0 (YFAS 2.0; Gearhardt, Corbin, & Brownell, 2016) is the most commonly used instrument to assess food-related addictive behaviours (Steward et al., 2018). This self-report questionnaire consists of 35 items scored on an 8-point Likert scale (from 0 = never to 7 = every day) and is adapted to assess addictive eating behaviours based on DSM-5 substance-related and addictive disorders criteria (APA, 2013). It refers specifically to consumption of foods high in fat, sugar, salt or refined carbohydrates. It

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3 includes items that assess specific criteria, such as diminished control over consumption, a
4 persistent desire or repeated unsuccessful attempts to quit, withdrawal, and clinically
5 significant impairment (i.e. 'I kept eating in the same way even though my eating caused
6 emotional problems'). The YFAS includes two scoring options: 1) a "symptom count" ranging
7 from 0 to 7 that reflects the number of addiction-like criteria endorsed and 2) a categorical
8 scoring option that classifies respondents as having either no, mild, moderate or severe
9 'food addiction'. The YFAS has received psychometric support in binge eating populations
10 (Gearhardt, White et al., 2013; Carter, Van Wijk & Rowsell, 2019), and obese bariatric
11 surgery patients (Clark & Saules, 2013; Meule, Heckel, & Kübler, 2012). The YFAS 2.0 was
12 developed to maintain consistency with the current diagnostic understanding of addiction
13 and to improve the psychometric properties of the original YFAS. Exceeding the food
14 addiction threshold was more strongly associated with obesity for the YFAS 2.0 than the
15 original YFAS. The YFAS 2.0 has demonstrated good internal consistency (Carter, Van Wijk &
16 Rowsell, 2019), as well as convergent, discriminant and incremental validity (Gearhardt,
17 Corbin & Brownell, 2016).
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23 (5) *Food intake in a Bogus Taste Test*

24 Actual food consumption will be measured by means of a Bogus Taste Test (Robinson et al.,
25 2017); a food consumption test presented under the guise of a taste test. Participants will
26 be instructed to rate 3 bowls of highly palatable high-calorie food items (chocolate, sweets,
27 crisps) in terms of their visual attractiveness, smell, and taste on a paper form. The
28 researcher will inform the participant that she/he will leave the room for 10 minutes and
29 during this time they can complete their ratings and are free to eat as much of the offered
30 items as they like. A small bin with lid will be provided and participants will be instructed to
31 consume as much food as they need or want, and to discard the remainder of the food
32 items in the bin before 10 minutes are over. After the participant has left, the discarded
33 food items will be recovered from the bin, sorted, and placed in their original bowls.
34 Consumption will be determined by weighing the bowls both before and after the "taste
35 test" and the difference in weight from pre-to post-assessment will be converted into
36 calories and used as a measure of food intake.
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42 (6) *Delay discounting*

43 Delay Discounting Task with Money and Food (Odum, Baumann, & Rimington, 2006):
44 Participants indicate their preferences in a series of choices for two hypothetical outcome
45 types: immediate versus delayed food and immediate versus delayed money. Participants
46 make choices involving either relatively small maximum amounts of food (10 dollars worth)
47 and money (10 dollars) or for relatively large maximum amounts of food (100 dollars worth)
48 and money (100 dollars). Performance on this task can be used to study self-regulation,
49 delayed gratification and valuation of reward. This task will be performed using Inquisit 5
50 (Millisecond Software).
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54 (7) *Inhibitory control*

55 (i) *Go/No-Go task*: The cued go/no go task is a useful measure of impulse control in clinical
56 populations. This task is a classic test of executive function, requiring effortful response
57 inhibition. The food specific version of the cued go no-go task (Teslovich et al., 2014)
58 measures impulsivity and response inhibition with respect to appetising food and nonfood
59 items (i.e. toys), via assessing the ability to inhibit instigated, prepotent responses. The task
60

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 set of stimuli consists of 30 colour images of common high- (8) and low-calorie (7) foods and common toys (15). The outcome variables include: (1) overall reaction time (RT) in milliseconds during correct “go” trials, (2) rate of omission errors (missed “go” trials), and (3) false alarm rate (rate at which participants erroneously press to a no-go stimulus). This task will be performed using Inquisit 5 (Millisecond Software).

(i) Stop Signal Task (SST): This is a task measuring inhibitory control. Participants are required to engage in a computer task but withhold their response in the presence of a stop signal. This SST includes food-specific and neutral non-food stimuli in the same task (adaptation of Manasse et al., 2016). This allows for isolation of any unique food specific inhibitory control deficits from general difficulties inhibiting responses. The outcome measure is the stop signal reaction time (SSRT). The SSRT is calculated for each set of stimuli (i.e., SSRT stimulus type) for each subject by subtracting the average stop signal delay from the average reaction time on “go” trials (Verbruggen & Logan, 2008). The recording accuracy of reaction time and stop signal delay measurement is in milliseconds. A smaller SSRT is indicative of greater inhibitory control and a larger SSRT reflects weaker/impaired inhibitory control. This task will be performed using Inquisit 5 (Millisecond Software).

(8) *Mood and emotion regulation*

The Emotion Regulation Questionnaire (ERQ) (Gross & John, 2003): 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). This will be administered at pre-assessment, post-assessment and follow-up.

Positive and Negative Affect Schedule (PANAS) (Watson, Clarke & Tellegen, 1988): The PANAS consists of two 10-item self-report scales which measure positive and negative affect. On a Likert scale ranging from 0 (very slightly or not at all) to 4 (extremely), participants rate the extent to which they have experienced each of the 20 descriptors within a particular time frame (“right now” in the current study). Two scores are generated: positive (PANAS-positive) and negative (PANAS-negative) affect. This will be administered at pre-assessment, post-assessment and follow-up.

Depression, Anxiety and Stress Scale (21-item version; DASS-21) (Lovibond & Lovibond, 1995): This is a 21 item self-report questionnaire which aims to evaluate mood, anxiety and stress levels over the previous week. The DASS-21 will be administered at pre-assessment, post-assessment and follow-up.

(9) *Within session measures (immediately after each [ABM+real/sham tDCS] treatment session)*

(i) Paper-based Visual Analogue Scales (VAS) assessing current hunger, feeling of fullness, urge to eat, urge to binge eat, feeling low, level of tension, level of stress, level of anxiety. These scales consist of a 10cm line. Participants are requested to indicate on this line a degree or level of a specific emotion or behavioural urge. There are indications of what range (e.g. from 'not at all' to 'extremely').

(ii) Tolerance, discomfort and side effects: An evaluation of discomfort with the training session (tDCS and ABM aspects separately) will be completed with another paper-based 10cm VAS (rated from none to extreme discomfort). Participants will be asked to report any side effects in an open ended question.

Appendix B: Information sheet for all participants

PARTICIPANT INFORMATION SHEET

ICARUS: An Investigation of Approach Bias Modification Training (ABM) and Transcranial Direct Current Stimulation (tDCS) in Binge Eating Disorder



IRAS Project ID: 244170

Research Ethics Committee reference number: 18/NW/0648

We would like to invite you to participate in this postdoctoral research project which 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. Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study. Please ask us if there is anything that is not clear or if you would like more information.

PART ONE

What is the purpose of the study?

Psychological therapy as a main treatment for Binge Eating Disorder (BED) may not be effective for many people and may not be readily accessible in some areas. Medical treatments for BED can have side effects and often do not remain effective in the long-term. Therefore, there is an ongoing need for the development of new treatments.

Computerised approach bias modification training (ABM) is a specific form of cognitive bias modification (CBM) that has been used to successfully treat mental disorders such as anxiety, depression, and addictive disorders. This technique involves several sessions of computerised training, a procedure which has shown to be effective in reducing the severity of some eating disorder symptoms in people with BED and Bulimia Nervosa (BN). ABM works as such; automatic approach and avoidance tendencies towards food-related cues are modified by repeated training of arm movements in front of a computer

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2
3 screen. ABM has shown to reduce approach tendencies and attention towards food cues
4 in a subclinical sample of eating disorders involving binge eating, but its efficacy on
5 these features in people with full-syndrome eating disorders remains unclear. Further
6 research is needed to examine if ABM is effective in reducing the frequency of binge
7 eating episodes in people with BED.
8
9

10 *Transcranial direct current stimulation (tDCS)* is a non-invasive technique that is capable
11 of stimulating specific brain areas. Research shows that the frontal areas of the brain
12 play a role in the development and maintenance of eating disorders, including BED.
13 Stimulating these brain areas to alter their functioning is therefore believed to have the
14 potential to reduce eating disorder symptoms. This involves the delivery of a low
15 electrical current via small electrodes placed on the scalp. This procedure is widely used
16 in research and is being applied in clinical settings. Recent research using tDCS on
17 people with BED has suggested that it may be helpful in reducing immediate food intake
18 and cravings, and may decrease the frequency of a desire to binge eat at home after the
19 treatment.
20
21
22

23 **Combining ABM and tDCS**

24 Previous studies suggest that these two techniques potentially help people better
25 regulate their behaviours through similar mechanisms in the brain. Delivering both
26 treatments together at the same time may have a stronger effect on reducing eating
27 disorder symptoms in people with BED than either of the treatments alone. This will be
28 the first time that this specific combination of interventions is conducted on people with
29 an eating disorder.
30
31

32 In the present study, we aim to investigate combined ABM and tDCS as a treatment for
33 BED by comparing the effect of 6 sessions of (ABM + real tDCS) vs. (ABM + placebo
34 tDCS) across a 3-week period in adult men and women with BED. We will also compare
35 these two groups against a control group. Participants will be allocated by chance to
36 either one of two intervention groups, or to the control group. Participants in the
37 intervention groups will receive 6 sessions of ABM delivered simultaneously with either
38 real tDCS or a placebo version of tDCS. Participants assigned to the control group will
39 not receive any intervention. We will measure eating disorder symptoms and other
40 outcomes in all participants at baseline, post-treatment, and at the 4-week follow-up to
41 assess outcomes of each study group. In particular, we are interested in changes in the
42 frequency of binge eating and craving, and thought processes and emotions related to
43 food and eating. We will also ask participants about their experience of this treatment.
44 Participants assigned to the control condition will be offered 6 sessions of (ABM + real
45 tDCS) after they have completed their involvement in the study.
46
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49

50 **Why have I been invited?**

51 You are invited to participate if you are a male or female aged between 18 and 70 who
52 has a current diagnosis of binge eating disorder (BED). We will be recruiting 66
53 participants in total.
54
55

56 **Do I have to take part?**

57 You do not have to take part in this experiment; it is your choice. If you decide to take
58 part, you will be asked to sign three identical consent forms. You will be free to
59
60

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3 withdraw from the study at any time without giving a reason. Whether you decide to
4 take part or not will in no way influence your care or the timing of your treatment.
5
6

7 **What will happen to me if I take part and what will I have to do?**

8 If you decide you want to participate you will firstly be asked to engage in a telephone
9 conversation with the researcher (lasting approximately 20 minutes) to confirm that
10 you are eligible to take part. If you are, you will be invited to the Institute of Psychiatry,
11 Psychology and Neuroscience (Kings College London, Denmark Hill Campus) for a
12 baseline assessment session on a day that is convenient for both you and the researcher,
13 in either the morning or the afternoon. On this day, the researcher will discuss the study
14 with you in person, answer your questions, and if you are happy to take part, we will
15 ask you to sign three copies of a consent form: one for you to keep, one for us to keep,
16 and one that will be sent to your general practitioner (GP).
17
18

19
20 This baseline assessment visit is longer than the treatment visits and is comprised of an
21 in-person visit and online questionnaires to complete at home. During the visit, you will
22 give informed study consent, complete two questionnaires, neuropsychological tasks
23 (brain puzzles), and a food task for which you will be asked to rate different foods. This
24 visit also involves an assessment version of the approach bias modification (ABM)
25 training programme, which is a computer based-task involving pushing and pulling a
26 joystick in response to shapes appearing on the computer screen. Weight and height
27 will be measured at each assessment, and participants may choose not to see the figures
28 recorded. Assessment visits will last 65-75 minutes. Within 36 hours after the in-person
29 visit, you will be emailed a link to a series of questionnaires (assessing mood and eating
30 disorder-related thoughts and habits) which will take 30-45 minutes to complete. There
31 is also the option to complete these assessment questionnaires in hardcopy paper
32 format.
33
34

35
36 You will then be then randomised and informed of your randomly assigned study
37 condition within a week. If you are assigned to one of the two intervention conditions,
38 you will be asked to attend 6 sessions where you will perform the ABM task while
39 receiving either real or placebo tDCS, in addition to completing the post-treatment and
40 follow-up assessments. If you are assigned to the control group, you will not receive any
41 intervention, and will be asked to attend the post-treatment and follow-up assessments.
42
43

44 All 6 intervention sessions will be identical and last approximately 40–50 minutes.
45 There is no need for any special preparation before the visits. Before and after each
46 intervention session, you will complete some scales related to aspects of your mood and
47 level of hunger. Your blood pressure and pulse will also be measured before and after
48 each intervention session to monitor your wellbeing.
49

50 During the (ABM + real/placebo tDCS) session you will sit on a comfortable chair facing
51 a computer screen, with a joystick on a table in front of you. You will wear a plastic
52 headband to keep the two tDCS electrodes in place (as shown in the diagram below).
53 The electrodes will be placed in small sponges soaked in a salt water solution, so they
54 might feel a bit wet against your head. The researcher will turn the machine on which
55 will deliver the currents. Depending on your assigned study condition, you will receive
56 real or placebo brain stimulation. The placebo session will be the same as the real
57 session, but the tDCS machine won't deliver any electrical current. Most people can't tell
58 the difference between real and placebo tDCS sessions.
59
60



The tDCS will begin a few minutes prior to the start of the computer training programme, to allow participants to become used to the sensation before starting the ABM task on the computer. The training version of the ABM programme is a computer based-task involving pushing and pulling a joystick in response to shapes appearing on the computer screen. The tDCS will also continue for a few minutes after the ABM task has ended. You will then be asked to rate any discomfort experienced during the session due the tDCS.

You will be asked to return to the Institute for 5 more identical intervention sessions within 3 weeks, leaving a gap of at least 24 hours between each session. The post-assessment will be conducted immediately after the 6th intervention session. This in-person visit comprising of the final intervention session plus the post-assessment will therefore last 90-120 minutes, with the online questionnaires to be completed within 36 hours after this visit (45 minutes). The follow-up assessment 4 weeks later will be similar to the baseline assessment. This final visit will therefore take 75 minutes, with the online questionnaires taking 45 minutes to complete at home afterwards.

20 participants (10 participants from each intervention condition) will be invited to provide feedback on their experiences of study participation, initial expectations of the intervention, perceived strengths and weaknesses, and suggestions for improvements in an interview with the researcher. Declining this invitation to interview does not affect study payment.

6 months after the baseline assessment, participants may be contacted by phone by a member of the King's College London Eating Disorders Unit for a brief phone call to evaluate the presence of eating disorder symptoms. This 6 month check-in will allow any long-term therapeutic effects of the study treatment intervention to be evaluated. Participation in this phone call will not affect participant payment, which will have been administered earlier after the 1-month follow up assessment.

Expenses and payments

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2
3 Upon completion of the study, all participants will be paid a maximum of £60 for
4 completing each of the three assessment sessions (comprised of an in-person visit and
5 at-home questionnaires); the baseline assessment, post-treatment assessment and
6 follow-up assessment (£20 each). This payment should be declared for tax and/or
7 benefit purposes. If you are assigned to an intervention condition involving 6 sessions
8 of brain stimulation and computer training, you may also be compensated up to £10 per
9 day for your travel expenses on these intervention session days.
10
11

12 **What is expected from you as a participant?**

13 We would expect you to complete all assessment sessions (pre-, post-treatment, follow-
14 up), and if you are randomised to an intervention group, to attend all 6 (ABM +
15 real/placebo tDCS) sessions as scheduled. We ask you to inform us immediately if for
16 any reason you suddenly find yourself unable to attend a scheduled session.
17
18

19 Please let us know of any health problem that has developed, or any new diagnosis
20 made since you enrolled for the study. Further, we would ask you to let us know of any
21 new medication or change in medication whilst you are taking part in the study.
22
23

24 **What are the possible disadvantages and risks of taking part? What are the side effects?**

25 Combined brain stimulation and cognitive training sessions are time-consuming and
26 may cause fatigue from concentrating on the task.
27
28

29 TDCS has been shown to be safe when used correctly in a clinical setting. However, you
30 may find the procedure slightly uncomfortable. This is because a number of sensations
31 can occur beneath the electrodes during stimulation including tingling, pain, itching,
32 and burning. Not everyone feels these sensations or finds them uncomfortable, but if
33 you do, remember you are free to stop the study at any point without giving an
34 explanation. In some rarer cases, tDCS has been known to cause a headache, but this can
35 be treated with mild painkillers (e.g. paracetamol). No side effects of ABM are known.
36 We will assess any discomfort you may experience during intervention sessions
37 throughout your involvement in the trial.
38
39
40

41 **What are the possible benefits of taking part?**

42 Unfortunately, there are no direct benefits to taking part in this study, but the
43 information we get may help us to improve the treatment of BED in the future.
44
45

46 **What happens when the research study stops?**

47 When the research study stops, no further ABM + tDCS sessions will be available to
48 those who have received 6 sessions. Participants in the control group will have the
49 option of receiving 6 sessions of [ABM + real tDCS] once they have completed the
50 waiting period and follow-up assessment.
51

52 Participants assigned to one of the intervention groups can request to be informed if
53 they had received ABM combined with real or placebo tDCS, once they have completed
54 the follow-up assessment.
55
56

57 **What if there is a problem?**

58 Any complaint about the way you have been dealt with during the study or any possible
59 harm you might suffer will be addressed. Detailed information on this is given in Part 2.
60

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making a decision.

PART TWO

What if relevant and new information becomes available?

Sometimes we get new information about the treatment being studied. This is not expected to occur given the short time frame of participation (6 sessions across 3 weeks); however, if any new and relevant information becomes available during this time we will inform you immediately. You can then decide whether you wish to continue in the study.

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

Your participation is voluntary and you do not have to take part in the study. You can change your mind at any point and terminate your participation without giving a reason to the researcher. You are free to withdraw from this study at any time without consequence.

Will participation in this study affect my routine healthcare, or the waiting period for treatment for my eating disorder if I am currently on a waiting list?

No. Participation in this study will have no impact on your treatment as usual, or waiting time if you are currently awaiting treatment for your eating disorder. We fully encourage you to begin treatment as provided by a health care professional as soon as it becomes available to you. We simply ask that you inform us of any changes to your treatment or medication while you are partaking in the study.

What if there is a problem?

If you have a concern about any aspect of the study, please ask the researcher (gemma.gordon@kcl.ac.uk, 0207 848 0183) who will do their best to answer your questions.

What if I wish to make a complaint?

If you remain unhappy and wish to formally complain, complaints to the IoPPN should be addressed to Dr Gill Dale. Director of Research Quality; Head, Joint R&D Office of South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology & Neuroscience (IoPPN), P005, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King's College London, De Crespigny Park, London SE5 8AF. NHS complaints will follow NHS complaints procedures.

Other sources of support for your eating disorder

To access support and treatment, please see your Eating Disorders clinician or your GP who will be able to advise you and refer you to the right service for you. You can also

1
2
3 obtain further information and support from www.beateatingdisorders.org.uk, the
4 national Eating Disorders charity.
5

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7 Should you wish to speak to someone outside of the university, please talk to your
8 Eating Disorders clinician, GP, the Beat helpline, and/or one of the study researchers
9 who is happy to liaise on your behalf if you so wish. The eating disorders charity Beat
10 provides helplines for adults and young people which offer support and information to
11 sufferers, carers and professionals. Further information can be found on their website
12 www.beateatingdisorders.org.uk, or by ringing their helpline 0808 801 0677.
13
14

15 **Will my taking part in the study be kept confidential?**

16 Your personal information and the data we collect from you will remain confidential at
17 all times. It will also remain anonymous to everyone apart from the primary
18 researchers. Manual files will be locked securely in a filing cabinet, which will be kept in
19 a locked office in the KCL Section of Eating Disorders, Department of Psychological
20 Medicine, IoPPN, and all electronic files will be password protected. All information
21 which is collected during the course of the research will be kept strictly confidential
22 according to the General Data Protection Regulation (GDPR), brought into effect on 25th
23 May, 2018. This new legislation creates some new rights for individuals to better reflect
24 data protection challenges in the modern digital age, as well as strengthening some of
25 the rights that currently exist under the Data Protection Act 1998.
26
27
28

29 **How will my personal data be used and what are my rights?**

30 King's College London is the sponsor for this study based in the United Kingdom. We
31 will be using information from you in order to undertake this study and will act as the
32 data controller for this study. This means that we are responsible for looking after your
33 information and using it properly. King's College London will keep identifiable
34 information about you for four years after the study has finished.
35

36 Your rights to access, change or move your information are limited, as we need to
37 manage your information in specific ways in order for the research to be reliable and
38 accurate. If you withdraw from the study, we will keep the information about you that
39 we have already obtained. To safeguard your rights, we will use the minimum
40 personally-identifiable information possible. You can find out more about how we use
41 your information by contacting the Study Coordinator Gemma Gordon.
42
43

44 KCL will use your name and contact details to contact you about the research study, and
45 make sure that relevant information about the study is recorded for your care, and to
46 oversee the quality of the study. Individuals from KCL and regulatory organisations may
47 look at your medical and research records to check the accuracy of the research
48 study. SLaM will pass these details to KCL along with the information collected from
49 you. The only people in KCL who will have access to information that identifies you will
50 be people who need to contact you regarding your participation or audit the data
51 collection process. The people who analyse the information will not be able to identify
52 you and will not be able to find out your name or contact details. KCL will keep
53 identifiable information about you from this study for four years after the study has
54 finished.
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56
57

58 **Involvement of the General Practitioner (GP)**

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60

As a matter of courtesy and in the interest of your wellbeing, we may let your GP know about your participation in the study, and may request your permission to send them a letter when you enroll. If you agree to this, you will be asked to provide us with your GP's contact details so that we can send them a letter with details of the research.

Insurance/indemnity

Standard KCL insurance and NHS indemnity arrangements apply.

Involvement of the insurance company

If you have private medical insurance, you should inform your insurance company that you are taking part in this study.

Will any genetic tests be done?

No.

What will happen to the results of the research study?

You will be offered the opportunity to be informed about your individual results once the data for all participants has been collected. If you want written feedback of the study's findings you can contact the researcher (gemma.gordon@kcl.ac.uk) for a lay summary. The results will be included in an examined postgraduate report, presented as part of a postgraduate presentation, and sent to a medical journal for publication. Your participation in the study will not be disclosed.

Who is organising and funding the research?

This study is being funded by King's College London.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by North West -Liverpool East Research Ethics Committee.

Further information and contact details

If you have any questions or require more information about this study, please contact the researcher using the following contact details:

Gemma Gordon (gemma.gordon@kcl.ac.uk) (0207 848 5608)
Section of Eating Disorders, Department of Psychological Medicine
KCL Institute of Psychiatry, Psychology and Neuroscience,
16 De Crespigny Park
London, SE5 8AF

Appendix C: Consent form for all participants

CONSENT FORM

IRAS Project ID: 244170

Research Ethics Committee reference number: 18/NW/0648

Please complete this form after you have read the information



sheet and listened to an explanation about the research.

Title of Study: ICARUS - An Investigation of Approach Bias
Modification Training (ABM) and Transcranial Direct Current
Stimulation (tDCS) in Binge Eating Disorder

Name of Researcher: Gemma Gordon



Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the information sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this consent form to keep and refer to at any time.

Please initial box

1. I confirm that I have read the information sheet dated 18.09.2018 (version 3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected.
3. 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 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.
4. I know that if I would like to, I can contact the research team and request a written summary of the study findings.
5. I understand that I must not take part if I have any of the conditions listed in the exclusion criteria.
6. I understand that during study participation, I must inform the researcher of any changes in my medication or of any new medical diagnoses made.
7. I agree to my General Practitioner (GP) being informed of my participation in this study.
8. I consent/do not consent to be contacted in the future by King's College London researchers who would like to invite me to participate in follow up studies to this project, or in future studies of a similar nature.
9. I agree to take part in the above study.

Participant's Statement:

I _____
 agree that the research project named above has been explained to me to my satisfaction
 and I agree to take part in the study. I have read both the notes written above and the
 Information Sheet about the project, and understand what the research study involves.

Signed**Date****Investigator's Statement:**

I _____
 Confirm that I have carefully explained the nature, demands and any foreseeable risks (where
 applicable) of the proposed research to the participant.

Signed**Date****For administration purposes, please indicate your preference below**

Q: In what format would you like to complete the at-home assessment questionnaires?

Tick '✓' in one box to indicate your choice

1. I would like to complete the assessment questionnaires online

2. I would like to receive a hardcopy paper version of the questionnaires in a
 stamped addressed envelope, to complete and post back to the researcher within
 36 hours of the in-person assessment visit.

Enquiries:

Gemma Gordon (gemma.gordon@kcl.ac.uk)
 Department of Psychological Medicine
 Section of Eating Disorders
 KCL Institute of Psychology, Psychiatry and Neuroscience,
 16 De Crespigny Park
 London, SE5 8AF
 Phone: 0207 848 5608

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For peer review only



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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____1_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_____1_____
Funding	4	Sources and types of financial, material, and other support	_____12_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____12_____
	5b	Name and contact information for the trial sponsor	_____12_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____12_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____11_____

1 **Introduction**

2

3 Background and rationale 6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention _____ 2-4 _____

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6 6b Explanation for choice of comparators _____ 4 _____

7

8 Objectives 7 Specific objectives or hypotheses _____ 4 _____

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10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) _____ 5 _____

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14 **Methods: Participants, interventions, and outcomes**

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16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained _____ 6 _____

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19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) _____ 5 _____

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22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered _____ 9-10 _____

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25 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) _____ 11 _____

26

27 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) _____ 11 _____

28

29 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial _____ 4, 11 _____

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32 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended _____ 6-9 _____

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1	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	___6__
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3				
4	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___5__
5				
6				
7	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___11__
8				
9				

10 **Methods: Assignment of interventions (for controlled trials)**

11 Allocation:

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13				
14	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	___5-6__
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20	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___6__
21				
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24	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___5__
25				
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27	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___5__
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31		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___6__
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35 **Methods: Data collection, management, and analysis**

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37	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___6-8__
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1		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____10-11_____
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4	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____10-11_____
5				
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8	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____10_____
9				
10				
11		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____10_____
12				
13		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____10_____
14				
15				
16				
17	Methods: Monitoring			
18				
19	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____10_____
20				
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25		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____11_____
26				
27				
28	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____11_____
29				
30				
31	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____n/a_____
32				
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35	Ethics and dissemination			
36				
37	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____1, 13_____
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1	Protocol	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes,	_____ 1, 12_____
2	amendments		analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals,	
3			regulators)	
4				
5	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and	_____ 12_____
6			how (see Item 32)	
7				
8		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary	_____ n/a_____
9			studies, if applicable	
10				
11	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained	_____ 10-11_____
12			in order to protect confidentiality before, during, and after the trial	
13				
14	Declaration of	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____ 12_____
15	interests			
16				
17				
18	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that	_____ 10_____
19			limit such access for investigators	
20				
21	Ancillary and post-	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial	_____ 11_____
22	trial care		participation	
23				
24				
25	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals,	_____ 1, 11_____
26			the public, and other relevant groups (eg, via publication, reporting in results databases, or other data	
27			sharing arrangements), including any publication restrictions	
28				
29		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ 12_____
30				
31		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ n/a_____
32				
33				
34	Appendices			
35				
36	Informed consent	32	Model consent form and other related documentation given to participants and authorised surrogates	_____ 24_____
37	materials			
38				
39	Biological	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular	_____ n/a_____
40	specimens		analysis in the current trial and for future use in ancillary studies, if applicable	
41				

1 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
2 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
3 [“Attribution-NonCommercial-NoDerivs 3.0 Unported”](#) license.
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For peer review only



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1 (no results)
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2-4
	2b	Specific objectives or hypotheses	4-5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9-10
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	5
	7b	When applicable, explanation of any interim analyses and stopping guidelines	11
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5-6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5-6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	n/a
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	n/a
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	n/a
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	n/a
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	n/a
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	n/a
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	n/a
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	n/a
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	12

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming; for those and for up to date references relevant to this checklist, see www.consort-statement.org.