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Title: High-Definition Transcranial Direct Current Stimulation in Anorexia Nervosa: A Pilot Study

Running Title: tDCS in Anorexia Nervosa

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The authors report no potential conflict of interest in relation to this work.

## Data Availability Statement

This paper describes a study protocol and thus, no data is available for this study.

Abstract

Anorexia nervosa (AN) is a serious psychiatric condition often associated with poor outcomes. Biologically informed treatments for AN, such as brain stimulation, are lacking, in part due to the unclear nature of the neurobiological contributions to the illness. However, recent research has suggested a specific neurobiological target for the treatment of AN, namely, stimulation of the inferior parietal lobe (IPL). The aim of this study is to stimulate - non-invasively - the left IPL in individuals with AN using high-definition transcranial direct current stimulation (HD-tDCS). Twenty participants will be randomised to receive 10 daily sessions of HD-tDCS or sham HD-tDCS (placebo). Assessments will be carried out at baseline and end-point, as well as 4- and 12-week follow-ups. This pilot investigation will primarily determine the feasibility and acceptability of this intervention.

Keywords: anorexia nervosa; eating disorder; brain stimulation; tDCS; parietal cortex; body image

Anorexia nervosa (AN) is considered a biopsychosocial condition, with biological, psychological and sociocultural factors postulated to contribute to illness development and maintenance (Phillipou, Musić, & Lee Rossell, in press). Despite AN being a condition that can result in serious psychological and physical outcomes, the mechanisms involved in the course of the illness are still poorly understood. In addition to the significant mortality and long-term morbidity associated with AN, the illness is associated with only a small window, early in the illness, for which current treatment options are most effective (Hay et al., 2014). Therefore, it is critical to establish more effective interventions for individuals at all stages of AN.

Unlike most other mental illnesses, interventions targeting underlying neurobiological dysfunction - including pharmacological treatments and brain stimulation techniques - are not

available to treat AN specifically. One of the reasons for this is that the neurobiological contributions to the illness have thus far not been fully elucidated (Phillipou, Rossell, & Castle, 2014). However, recent findings from our research group have indicated specific brain regions of potential dysfunction in AN, providing possible targets for treatment. In this research, we identified very distinctive eye movement abnormalities in individuals with AN (Phillipou, Rossell, Castle, Gurvich, & Abel, 2014). Although eye movement assessment may not appear to be an obvious tool in the investigation of the neurobiology of mental illness, eye movements are subserved by very well-defined neural circuitry, and specific deficits in the generation of eye movements can identify specific brain regions and/or neurotransmitters involved in an illness.

In our previous research, eye movement abnormalities, called square wave jerks (SWJs; small, involuntary and unconscious side-to-side eye movements), were uncovered while AN participants were fixating on a central stimulus (Phillipou, Rossell, Castle, et al., 2014). Notably, the rate of these atypical eye movements, in combination with level of anxiety, predicted group membership (i.e. AN or healthy control) with exceptionally high accuracy, suggesting it is a unique biomarker for the illness. SWJs were not, however, associated with illness duration, body mass index or eating behaviours, which is advantageous as it suggests that this proposed biomarker may not be influenced by the effects of starvation (Phillipou, Rossell, & Castle, 2018). Importantly, SWJs showed an inverse relationship with anxiety. As an *increased* rate of SWJs was associated with *low* anxiety (and vice versa), the presence of anxiety did not to contribute to this biomarker, but specifically, the relationship that anxiety levels had with SWJ rate in people with AN. We have speculated

that this relationship may be related to gamma-aminobutyric acid (GABA) concentrations in the brain as alterations of this neurotransmitter contribute to both SWJs and anxiety (Munoz & Wurtz, 1993; Nemeroff, 2003). Specifically, these eye movements are indicative of altered functioning of the superior colliculus (SC), and GABA-ergic neurones in this area (Munoz & Wurtz, 1993). The contribution of anxiety, however, as well as the neural underpinnings of this biomarker remain unresolved, and it should also be noted that this biomarker is yet to be replicated in the literature.

The SC is a midbrain region which plays a key role in the eye movement system, receiving inputs from different brain regions, including the left inferior parietal lobule (IPL), via the substantia nigra (SN; also in the midbrain) to initiate and inhibit eye movements. Findings from our pilot research have also indicated reduced functional connectivity between these midbrain regions and the left IPL in individuals with AN, suggesting reduced communication between these brain areas (Phillipou et al., 2019). This is an important finding as these brain regions are involved not only in eye movement production, but also in multi-sensory integration and body image, key deficits in which are arguably the driving-force behind AN behaviour (Phillipou, Castle, & Rossell, 2018). As the IPL and midbrain regions showed reduced communication in AN, stimulating these regions may promote better functional connectivity, and consequently reduce symptomatology in AN. The relationship of this eye movement abnormality to underlying illness mechanisms and the possibility that altering these neural circuits will provide therapeutic benefit, however, remain theoretical and require further investigation.

Non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and high-definition tDCS (HD-tDCS; more focal stimulation), have been widely used in other psychiatric illnesses. In particular, a large of body of literature exists demonstrating the efficacy of repetitive TMS (rTMS) for the treatment of depression (Gaynes et al., 2014). Indeed, rTMS is a US Food and Drug Administration (FDA)–approved treatment for major depressive disorder. Although TMS is a non-invasive brain stimulation technique, it is associated with a number of potential risks, such as fainting and seizures. Given the physical complications associated with starvation in AN, utilising a technique with reduced physical risks, such as tDCS, would be beneficial.

In contrast to TMS, tDCS does not evoke action potentials but induces a change in the membrane potential, i.e. anodal stimulation causes membrane depolarisation and increases the propensity for neuronal firing, whereas cathodal stimulation decreases the likelihood of neuronal activity. In the first published study employing tDCS in AN, Khedr, Elfetoh, Ali, and Noamany (2014) stimulated the left dorsolateral prefrontal cortex (DLPFC) with anodal tDCS in seven treatment-resistant AN patients. Five patients showed improved eating disorder and depressive symptoms immediately following a 10-day course of tDCS, two of whom maintained this improvement at one-month follow-up. Similarly, Strumila et al. (2019) stimulated the left DLPFC with tDCS over 20 sessions (twice daily for 10 days) in a sample of nine AN patients and found reduced eating disorder and depressive symptoms following the intervention and at one-month follow-up. Costanzo et al. (2018) also stimulated the left DLPFC with tDCS in a group of 11 participants (three sessions a week, for six weeks), but also included a comparison group of 12 AN patients who received family based therapy

(FBT) in an open label study. Although no group differences were reported in eating disorder symptoms, body mass index (BMI) was reported to significantly increase in the tDCS group but not in the FBT group. In addition, TMS over the left DLPFC has also been associated with reduced AN symptomatology (McClelland et al., 2016; Van den Eynde, Guillaume, Broadbent, Campbell, & Schmidt, 2013). Justification for stimulating the left DLPFC in AN is, however, based largely on studies in major depressive disorder, which typically stimulate this site, rather than neurobiological findings in AN. Furthermore, given the small number of study using tDCS or TMS in AN, further research is required to determine the efficacy of these treatments.

The aim of this pilot investigation is to non-invasively stimulate the left IPL with HD-tDCS in individuals with AN. The primary outcomes of the study will be to assess feasibility and acceptability of the intervention, namely, to assess: recruitment rates, retention rates, and acceptability in terms of compliance with the proposed schedule and adverse events. The secondary objectives of the trials are exploratory, and will assess clinical outcomes from baseline to end-point, including Eating Disorder Examination Questionnaire (EDE-Q; short form) total scores, AN symptom scale scores (adapted from McClelland et al. (2016); Likert scale ratings including urge to eat, urge to exercise, urge to restrict, feeling of fatness, feeling of fullness, mood and anxiety) and SWJ rate during a fixation task. Additional exploratory outcome measures will include physical measurements (including body mass index) and resting state functional connectivity of the left IPL from baseline to treatment end-point, as well as assessments that have previously been reported in the literature as characteristic of AN including a battery of eye movement tasks (Phillipou et al., 2015; Phillipou, Rossell,

Gurvich, Castle, & Abel, 2016; Phillipou, Rossell, Gurvich, Castle, Troje, et al., 2016; Phillipou, Rossell, Gurvich, Hughes, et al., 2016) and set-shifting (i.e. the Wisconsin Card Sorting Test) (Steinglass, Walsh, & Stern, 2006). Follow-up assessments will also be completed at 4- and 12- weeks post-intervention.

## Methods

The trial has been registered with the Australian & New Zealand Clinical Trials Registry (ANZCTR; ACTRN12618001966280) prior to the enrolment of any participants (05/12/2018).

### *Design*

AN patients will be randomised to receive either active HD-tDCS or sham (placebo) HD-tDCS to the left IPL. Randomisation will be performed independently of the researchers by an independent researcher using block randomisation (2 x 4) with a 1:1 allocation, and will be concealed from the participants and the investigators performing the analyses. The investigator administering the intervention will not be blinded to group allocation due to the nature of the technology, which is a potential limitation of this study design.

The randomisation information will be maintained by the independent researcher until data collection is complete. An emergency code break envelope will be provided to the principal investigator which will only be opened in the case of an emergency, such as a serious adverse event that requires the knowledge of the treatment being taken to manage the participant's condition.

Daily HD-tDCS (or sham HD-tDCS) will be administered for 10 days (on weekdays only) and will involve anodal HD-tDCS applied to the left IPL for 20 minutes at 2mA (plus 30s ramp up and 30s ramp down). Sham HD-tDCS will be administered in the same manner, but will ramp down following the initial 30s ramp up period, and will similarly ramp up and down at the end of the 20 minutes of sham stimulation. HD-tDCS will be administered by a trained investigator with the Soterix HD-tDCS system (HD-tDCS adaptor, model 4X1-C3A; controlled with the 1x1 tDCS system, model 1300A) using an electrode cap. A 4x1 electrode montage (based on the standard 10-20 system) will be used, with the central electrode position at P3 (anodal), and four surrounding electrodes (cathodal at CP3, P1, P5, PO3), enabling focal anodal stimulation of the left IPL (P3). While participants are receiving HD-tDCS or sham HD-tDCS, they will be viewing visual noise on a computer monitor.

Baseline assessments will be completed on Day 1 of the trial, before the first administration of HD-tDCS. Participants will also complete assessments at the end of the intervention (endpoint; post-HD-tDCS), and at 4- and 12-week follow-up (see Table 1). Baseline, end-point, and follow-up assessments will take place at Swinburne University. Daily HD-tDCS sessions will take place at Swinburne University, St Vincent's Hospital, or The Melbourne Clinic, as preferred by the participant.

*Participants*

Twenty participants with AN will be recruited for this study. Recruitment sites will include The Melbourne Clinic (TMC) and the intensive day patient program run at the Body Image & Eating Disorders Treatment & Recovery Service (BETRS) at St Vincent's Hospital,

Melbourne. A member of the research team at BETRS/TMC will identify potential participants, and approach them with the study information form. Participants will also be recruited through public advertisements and established participant registries, including the Body Image Disorders Participant Registry at Swinburne University. Potential participants will initially be screened to assess their eligibility. Those who pass the screen will be sent a copy of the site-specific Participant Information and Consent Form (PICF) and asked to read it carefully prior to attending the baseline assessment. Written informed consent will be obtained from all participants by a researcher who is not involved in treating the patient prior to their participation at the baseline session.

Inclusion criteria for participation will include being female, right-handed, English speaking, and over 18 years of age; and with a current diagnosis of AN according to DSM-5 criteria (BMI under 18). All participants will be required to have ongoing medical support during the course of the intervention. All participants will also be required to be medically stable and on a medication regime that has been stable for at least one month prior to inclusion in the study.

Participants will not be included in the study if they are on medications that lower seizure threshold, have a comorbid psychotic condition, substance/alcohol dependence, a history of neurological illness or head injury, or any significant ocular pathology. Participants must not be undergoing any brain stimulation intervention currently, or in the past year. As participants will be required to undergo an MRI, a number of further exclusions for safety purposes will be required including, that the participant is not pregnant or breastfeeding, they

do not have any irremovable metal (ferromagnetic metals) in their body that poses a safety concern and do not suffer from claustrophobia.

*Safety*

HD-tDCS is not associated with significant risks to participants. HD-tDCS involves a low direct current that is delivered via electrodes to the head to non-invasively stimulate the brain. Participants may experience mild tingling sensations under the electrodes during HD-tDCS and it may cause headache. No serious adverse events have been reported using HD-tDCS.

Participants will also be required to complete an adverse events measure at each assessment session to ascertain any adverse events (AEs). All AEs will be recorded in the adverse event log in the participant case report form (CRF), including the seriousness, severity, relationship to study product, duration, and outcome. In all cases, researchers will maintain contact with participants who experience an AE until it has been resolved and symptoms disappear. They will also be asked to notify their treating physician.

*Outcome Measures: Feasibility and Acceptance*

Feasibility will be assessed in terms of recruitment numbers, with success defined as 20 participants enrolled over a period of 18 months and successful retention rates defined as less than 20% drop-out. Acceptability of the intervention will be assessed in terms of adverse events and fidelity to the protocol, as defined by protocol violations.

*Additional Measures*

The CRF will be completed at baseline and will include the collection of basic demographic information and a brief medical history. Physical measurements will also be collected using the Tanita Body Composition Scale. The Wechsler Test of Adult Reading (WTAR) will be used to estimate premorbid intelligence (Wechsler, 2001), and the Mini International Neuropsychiatric Interview (MINI) 7.0.2 for DSM-5 will be administered to confirm AN diagnoses (with the exception of BMI <18 rather than <17) and to gather detailed information about comorbid conditions (Sheehan et al., 1998). Participants with comorbid conditions will be included in the sample to ensure a representative sample of AN participants is assessed. The remainder of the CRF will include self-report assessments completed by the participant on an iPad through the Qualtrics platform (please see Table 1 for a list of measures).

At baseline, participants will also complete a battery of saccadic eye movement tasks administered and recorded with the EyeLink Portable Duo at 1000Hz (SR Research, Ontario, Canada), with the use of a chinrest (see Table 2 for task descriptions). Participants will also complete the Wisconsin Card Sorting Test (WCST) through the platform Millisecond, as a measure of set-shifting ability. In addition, participants will undergo a magnetic resonance imaging (MRI) scan that will involve high-resolution structural scans as reference scans (T1 and diffusion-weighted scans, at one timepoint only), as well as a resting state functional MRI (fMRI) scan and an arterial spin-labeled perfusion scan (both used for functional

connectivity analyses). The two functional scans will require participants to look at a white fixation cross against a black background for the entire duration of the scans.

End-point assessments will be completed following the last session of HD-tDCS (see Table 1 for details). Participants will also be asked to indicate whether they believe they were receiving active or sham HD-tDCS. Follow-up sessions will take place 4 weeks and 12 weeks following the final HD-tDCS session, in which all baseline assessments will be repeated except the MRI scans, WTAR, EHI and STAI (trait).

*Analysis*

*Data analysis*

Eyetracking data will be analysed with SR Research's program DataViewer, and custom-made programs in Matlab and Microsoft Excel (see Table 2 for outcome measures for each task). MRI data will be analysed with specialised toolboxes in Matlab, including Statistical Parametric Mapping (SPM) the CONN functional connectivity toolbox. Whole brain functional connectivity analyses will be undertaken for the ASL and resting state scans, as well as region-of-interest analyses focusing on the left IPL. The WCST will be analysed for total errors, perseverative errors, perseverative responses, categories completed and failure to maintain set.

*Statistical analysis*

The primary outcomes assessing feasibility and acceptance of the intervention will be reported with descriptive statistics. The exploratory, secondary objectives of the trial will be

analysed with mixed design analyses of variance (ANOVAs) to compare active HD-tDCS and sham tDCS groups between baseline and end-point assessments, and follow-up assessments. Exploratory correlational analyses will also be undertaken between the variables.

## Conclusion

AN is a significant mental illness associated with high morbidity and mortality rates. The development of more effective treatments is urgently required. This pilot investigation will provide preliminary evidence to determine the feasibility and acceptability of non-invasively stimulating the left IPL in individuals with AN with HD-tDCS. Specifically, this study will inform whether this is a viable intervention that should be subjected to a randomised controlled trial (RCT). Current treatments for AN are costly, with many patients receiving treatment over many years, and a large proportion not achieving recovery at long-term follow-up. Brain stimulation techniques such as HD-tDCS, which are non-invasive and are associated negligible risks, provide a promising potential therapeutic tool for the treatment of AN, if found to be successful. In addition to posing minimal physical risks, the duration of HD-tDCS treatment has the potential to be significantly shorter (i.e. 10 daily sessions) than that required for psychological therapies for AN such as cognitive behaviour therapy (CBT) (i.e. 20 sessions over 20 weeks is recommended). The potential utility of HD-tDCS as a stand-alone treatment or as a potential adjunct therapeutic intervention for AN is yet to be determined; therefore, requiring further investigation.

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Table 1: Study procedure and assessments

| | Assessment/Procedure | Description | Enrolment | Visit 1 (Baseline) | Visit 2-9 (HD-tDCS) | Visit 10 (End-point) | Follow-up 1 (4 wks post end-point) | Follow-up 2 (12 wks post end-point) |
|---|---|---|---|---|---|---|---|---|
| **Procedures** | **Screening for eligibility** | Inclusion/exclusion criteria screening | x | | | | | |
| | **Allocation** | Group allocation (active/sham) | x | | | | | |
| | **Informed Consent** | Written informed consent | | x | | | | |
| | **tDCS Safety Form** | Safety checklist to undergo tDCS | | x | | | | |
| | **MRI Safety Form** | Safety checklist to undergo MRI | | x | | x | | |
| | **Clinical Demographic Form** | Basic demographic information and brief medical history | | x | | x | x | x |
| | **Physical Measurements (Tanita Body Composition Scale)** | Body mass index, body fat %, body water %, muscle mass, bone mass, physique rating, basal metabolic rate, visceral | | x | | x | x | x |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | fat rating, metabolic age | | | | | |
| | **Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001)** | Measure of premorbid intelligence | **x** | | | | |
| | **Mini International Neuropsychiatric Interview (MINI) 7.0.2 (Sheehan et al., 1998)** | Psychiatric diagnoses | **x** | | | **x** | **x** |
| | **Edinburgh Handedness Inventory (EHI) (Oldfield, 1971)** | Determine handedness | **x** | | | | |
| | **AN symptom scales (McClelland et al., 2016)** | Likert scale ratings including urge to eat, urge to exercise, urge to restrict, feeling of fatness, feeling of fullness, mood and anxiety | **x** | | **x** | **x** | **x** |
| | **Eating Disorders Examination Questionnaire (EDE-Q) (Fairburn, 2008)** | Eating disorder symptomatology over the previous four weeks | **x** | | | **x** | **x** |
| | **Eating Disorder Examination Questionnaire – Short Form (EDE-QS) (Gideon** | Eating disorder symptomatology over the previous week | **x** | | **x** | **x** | **x** |

| | | | | | | |
|---|---|---|---|---|---|---|
| | **et al., 2016)** | | | | | |
| | **Stunkard Figure Rating Scale (FRS) (Stunkard, 1983)** | Assessment of body image in which 'ideal', 'thought' and 'felt' body sizes are chosen from a series of silhouettes | **x** | **x** | **x** | **x** |
| | **Dysmorphic Concern Questionnaire (DCQ; modified for one week): (Mancuso, Knoesen, & Castle, 2010)** | Body dysmorphic concern over the previous week | **x** | **x** | **x** | **x** |
| | **Depression Anxiety Stress Scale (DASS-42) (Lovibond & Lovibond, 1995)** | Symptoms of negative mood over the previous week | **x** | **x** | **x** | **x** |
| | **State Trait Anxiety Inventory (STAI) (Spielberger, 2010)** | Assessment of state and trait anxiety | **x** | **x** | **x** | **x** |
| | **Assessment of Quality of Life (AQoL-8D) (Richardson, Iezzi, Khan, & Maxwell, 2014)** | Quality of life assessment over the previous week | **x** | **x** | **x** | **x** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Eyetracking** | See Table 2 for task details | **x** | | **x** | **x** | **x** |
| | **Wisconsin Card Sorting Test (WCST)** | Measure of set-shifting | **x** | | **x** | **x** | **x** |
| | **Magnetic Resonance Imaging (MRI)** | Structural and functional scans | **x** | | **x** | | |
| | **High-Definition Transcranial Direct Current Stimulation (HD-tDCS)** | Administered to the left inferior parietal lobe | **x** | **x** | **x** | | |
| | **Adverse Event Log** | Adverse events and severity following HD-tDCS | **x** | **x** | **x** | | |

Table 2: Saccadic Eye Movement Tasks

| Task | Description | Outcomes |
|---|---|---|
| Fixation | Black fixation cross in the centre of a white screen for one minute. This task will be repeated three times (i.e. 3x1 minute blocks) | Direction, amplitude/size and intersaccadic interval of SWJs |
| Prosaccade | Black dots will be presented at ±5, 10 and 15° horizontally on a white screen and will require the participant to simply look at the targets when they appear. Each trial will begin with a fixation cross in the centre of the screen | Error rate, and latency, gain/accuracy and peak velocity of correct |

| | | |
|---|---|---|
| | | prosaccades |
| Antisaccade | Presented in the same manner as the prosaccade task (i.e. fixation cross in the centre, dot in the periphery at ±5, 10 and 15°) but when the target dot is presented, participants will be required to look immediately at the dot's mirror image (same distance from the centre but in the opposite direction) | Error rate, and latency, gain and peak velocity of correct antisaccades |
| Memory-guided/ oculomotor delayed response | Participants will be fixating on a fixation cross in the centre of the screen while a dot is briefly (50ms) presented in their periphery (±5, 10 and 15° horizontally). Participants will be required to continue fixating on the cross and not look at the dot when it appears. After a short delay, the fixation cross will disappear and participants will be required to look at where they remember the dot appearing. | Directional errors (looking in the wrong direction to where the stimulus was presented) and inhibitory error rate (looking at the stimulus when it was presented), and gain, latency and peak velocity of correct memory-guided saccades |
| Visual scanpaths | Participants will be presented with images of landscapes and geometric shapes (non-emotive stimuli) and will be required simply to look at the stimuli as they appear. Following the presentation, participants will be required to indicate with a mouse click whether the image they just saw was an image of a landscape or geometric shapes (this component of the task was designed to ensure participants remain attentive to the stimuli) | Number of and duration of fixations, and saccade amplitudes |

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