A randomised controlled feasibility trial of intermittent theta burst stimulation with an open longer-term follow-up for young people with persistent anorexia nervosa (RaISE)

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RESEARCH ARTICLE

A randomised controlled feasibility trial of intermittent theta burst stimulation with an open longer-term follow-up for young people with persistent anorexia nervosa (RaISE): Study protocol

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Abstract

Objective: We present the protocol of a feasibility randomised controlled trial (RCT) of intermittent theta burst stimulation (iTBS) for young people with anorexia nervosa (AN). Effective first-line psychological therapies exist for young people with AN, but little is known about how to treat those who do not respond. Non-invasive neuromodulation, such as iTBS, could address unmet treatment needs by targeting neurocircuitry associated with the development and/or maintenance of AN.

Design: Sixty-six young people (aged 13–30 years) with persistent AN will be randomly allocated to receive 20 sessions of real or sham iTBS over the left dorsolateral prefrontal cortex in addition to their usual treatment. Outcomes will be measured at baseline, post-treatment (1-month post-randomisation) and 4-months post-randomisation (when unblinding will occur). Additional open follow-ups will be conducted at 12- and 24-months post-randomisation. The primary feasibility outcome is the proportion of participants retained in the study at 4-months. Secondary outcomes include AN symptomatology, other psychopathology, quality of life, service utilisation, neurocognitive processes, and neuroimaging measures.

Discussion: Findings will inform the development of a future large-scale RCT. They will also provide exploratory data on treatment efficacy, and neural and neurocognitive predictors and correlates of treatment response to iTBS in AN.

Amelia Hemmings and Lucy Gallop have contributed equally to this work and share first authorship.

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KEYWORDS
anorexia nervosa, eating disorders, feasibility randomised controlled trial, intermittent theta burst stimulation, neuromodulation

HIGHLIGHTS

- This paper presents a study protocol of a triple-blind feasibility randomised controlled trial (RCT) with an open longer-term follow-up, using intermittent theta burst stimulation (iTBS) for young people with AN.
- It provides a clinical and scientific rationale for conducting a neuromodulation RCT in eating disorders.
- It is hoped that the findings will inform the development of a future large-scale RCT investigating the clinical efficacy of iTBS for AN.

1 | INTRODUCTION

Anorexia nervosa (AN) is a life-threatening illness, affecting up to 2.5% of young people of all genders (Silén & Keski-Rahkonen, 2022). AN typically develops in adolescence or emerging adulthood, with an 18% onset by age 14, 55% by 18, and 79% by 25, and a median age at onset of 17 years (Solmi et al., 2022). This spans a period of important changes in neural, cognitive, and socio-emotional development that continues into early adulthood (i.e., mid-to-late 20s; (Riedel et al., 2022)). Cumulative neural changes arising from prolonged starvation and from social disruption during emerging adulthood are likely to have detrimental impacts on the course of illness (Treasure et al., 2015). It is important to recognise that as the duration of illness lengthens, the future odds of a stable, strong recovery lessen (Eddy et al., 2017) and the risk of developing a persistent form of illness increases.

The efficacy of psychological treatments for adults with AN is low to moderate (Solmi et al., 2021), with randomised controlled trials (RCTs) of psychological therapies for adults with AN demonstrating remission rates between 13% and 43% (Brockmeyer et al., 2018). For adolescents, family therapy for AN (FT-AN) has been associated with favourable results compared to individual therapy (e.g., Hay, 2013). Estimates of remission rates for FT-AN for adolescents are around 50% (Lock, 2011), though there is significant variability according to the definition of remission used, that is, between 21.7% and 87.7% (Le Grange et al., 2019). For those for whom FT-AN is not effective, there are no specific superior treatments associated with positive longer-term outcomes (Solmi et al., 2021). There is, therefore, a significant proportion of individuals who remain at risk of progressing into a more persistent course of illness (Fichter et al., 2017). Pharmacological interventions are not well established for this group. Overall, there is a demand for novel interventions to address unmet treatment needs in adolescents and young adults with AN.

The aetiology of AN is complex and multi-factorial. Most neurobiological models propose that there is a problem between "bottom-up" subcortical emotional and reward-related brain regions, and "top-down" cognitive control-related circuitry in prefrontal regions (e.g., O'Hara et al., 2015; Steinglass & Walsh, 2016). Clinically, alterations in these neural circuits present as changes in reward processing, cognitive control, socio-emotional processing, appetitive regulation, negative affect, and stress responsivity (Frank et al., 2019; Kaye et al., 2009; Simon et al., 2019). Specifically, the dorsolateral prefrontal cortex (DLPFC) is a functionally and structurally heterogeneous region implicated in dysfunctional self-regulatory and cognitive control processes in AN, including inhibitory control, food choice, and reward processing (Dunlop et al., 2016; Monteleone et al., 2017; Simon et al., 2019; Val-Laillet et al., 2015). The DLPFC is densely connected to limbic regions, including the anterior cingulate cortex (ACC) and amygdala, and it has been proposed that in AN, the degree of DLPFC-amygdala functional connectivity correlates with emotion regulation abilities (Steward et al., 2022). It is plausible, therefore, that neural changes, in combination with the egosyntonic nature of the disorder (i.e., wherein individuals with AN value the disorder, thereby reducing motivation for recovery (Gregertsen et al., 2017)), serve to maintain the illness and contribute to the limited effectiveness of psychological therapies. In these circumstances, treatments that seek to directly modify brain activity and induce functional (neuroplastic) changes in illness-associated brain regions and networks are a promising new approach to explore.

Neuromodulation is increasingly being explored for the treatment of AN (Gallop et al., 2022). Repetitive transcranial magnetic stimulation (rTMS) is a neuromodulation technique employing brief magnetic pulses,

delivered via an electromagnetic coil placed on the scalp, to modulate cortical excitability in targeted AN-relevant brain regions. Cortical excitability can be increased or suppressed with high (>5 Hz; HF-rTMS) or low (<1 Hz) frequency rTMS, respectively (Fitzgerald et al., 2006). rTMS has a larger evidence-base than other neuromodulation techniques in AN (Kim et al., 2023), with various case studies, series and single-session RCTs reporting improvements in AN symptoms and/or BMI (Choudhary et al., 2017; McClelland et al., 2013; McClelland, Kekic, Bozhilova, et al., 2016; McClelland, Kekic, Campbell, & Schmidt, 2016; Van den Eynde et al., 2013). These studies applied HF-rTMS over the left DLPFC, based on the association between DLPFC function and AN symptomatology (e.g., Dunlop et al., 2016) and the dense connectivity between the DLPFC and AN-relevant, deeper limbic brain regions like the amygdala, ACC, and insula (e.g., Seidel et al., 2018; Steward et al., 2022). It is proposed that emotion regulation and reappraisal processes involve prefrontal cognitive control areas, such as the DLPFC, modulating activity in subcortical systems that generate emotional responses (Ochsner et al., 2012). Excitatory rTMS for AN may therefore be strengthening the top-down cognitive control of the DLPFC on limbic regions such as the amygdala, aiding with emotion regulation and possibly reducing fears around food. The left DLPFC has been the most investigated potential target and, therefore, has the most supporting evidence (Gallop et al., 2022). A key proposed mechanism of HF-rTMS to the left DLPFC is positive effects on emotion regulation, with Lantrip et al. (2019) comparing left and right DLPFC stimulation in healthy women and finding that emotion regulation was improved following left and not right DLPFC rTMS. Other research has used HF-rTMS applied to alternative neural targets for AN, for example, the dorsomedial PFC, for binging behaviours (Dunlop et al., 2015) and for co-morbid depression and post-traumatic stress disorder (Woodside et al., 2021), and the right DLPFC, for increasing food choice flexibility (Muratore et al., 2021).

The TIARA study, the first randomised sham-controlled trial of HF-rTMS to the left DLPFC in adults with persistent AN (average illness duration ~14 years and multiple previous treatments), reported medium to large between-group effect sizes in mood and quality of life, favouring real rTMS at 4-months post-randomisation (Dalton et al., 2018). In the 18-month open follow-up, a medium between-group effect was reported for BMI change, as well as a higher rate of weight recovery in the real rTMS group compared to sham [46% versus 9% (Dalton et al., 2020a)]. This corresponded with participants self-reporting increased flexibility around food (Dalton et al., 2022), and was consistent with data from the food choice task (see Steinglass et al., 2015 for task methodology) that showed a decrease in self-controlled food choices at post-stimulation compared to baseline (Dalton et al., 2020b). Findings suggest that improvements in mood and food choices following rTMS precede the weight gain observed in the longer term in adults with persistent AN (Dalton et al., 2020a).

As part of the TIARA trial, arterial spin labelling (ASL) was used to quantify TMS-related changes in regional and global cerebral blood flow (CBF). A significant treatment-by-time interaction indicated a greater reduction in CBF in the right amygdala following real rTMS compared to sham. In addition, participants with the most significant rTMS-related reduction in amygdala CBF showed the greatest sustained weight gain at 18-month follow-up. Higher CBF in the insula at baseline also predicted greater weight gain between baseline and 4-months post-randomisation, providing a potential candidate for a biomarker of rTMS treatment response in this patient group (Dalton et al., 2021). However, further research is needed to establish the neural predictors and correlates of rTMS treatment in AN. In major depressive disorder (MDD), growing evidence suggests that rTMS treatment response is associated with lower baseline functional connectivity between the subgenual anterior cingulate cortex (sgACC) and the DLPFC in adults (e.g., Chou et al., 2021; Ge et al., 2020) and adolescents (Tapia Palacio, 2021). Connectivity between the sgACC-DLPFC has not been examined in relation to rTMS response in AN, although preliminary evidence suggests that rTMS may increase the top-down regulation of the DLPFC on limbic areas, such as the amygdala (Dalton et al., 2021). It is possible to create several hypotheses regarding how rTMS would change behaviour and neural activity because little is known about the associated neurophysiology. However, it is reasonable to hypothesise that repeatedly stimulating the DLPFC will induce some form of long-term potentiation in the system, that is, it will make the system more functionally connected. In this respect, this would explain our preliminary data on the observed decreased amygdala activation (Dalton et al., 2021).

Adoption of rTMS in clinical settings is hindered by high costs and low capacity in services (Blumberger et al., 2018). The conventional NICE-approved protocol requires 37.5 min of HF-rTMS stimulation per session, whereas newer forms of rTMS, for example, theta burst stimulation (TBS), take less than 4 min to administer. Like HF- or LF- rTMS, TBS can be used to either facilitate (intermittent TBS) or inhibit (continuous TBS) cortical activity, depending on the stimulation pattern. Compared to HF-rTMS, iTBS requires a lower stimulation intensity (80% vs. 120% of resting motor threshold), is reported to

have longer-lasting effects on brain plasticity (Noh et al., 2012), and is non-inferior in treating adults with MDD (Blumberger et al., 2018). The therapeutic effects of iTBS have yet to be examined in adolescents and/or young adults with AN, but evidence suggests that iTBS is an effective treatment option for young people with MDD (Dhami et al., 2019). Therefore, TBS may be a safer and more cost- and time-effective neuromodulation choice for young people with AN. The present study aims to transcend traditional age boundaries by designing interventional research based on specific developmental periods (i.e., adolescence and emerging adulthood) rather than arbitrary age cut-offs between children and adults. We will investigate the feasibility of comparing real versus sham iTBS-treatment, delivered to the left DLPFC in young people with persistent AN.

1.1 | Study aims

The primary aim of this study is to investigate the feasibility of iTBS as a treatment for young people with AN, to acquire information to develop a large-scale RCT of therapeutic iTBS in this population. Our primary feasibility outcome is retention of trial participants at 4-months post-randomisation.

Secondary aims include:

1. Assessing acceptability, credibility, recruitment, and attendance.
2. Determining the best outcome measures for a full trial by examining the quality, completeness, and variability in the data.
3. Assessing the safety of iTBS for young people, via cardiac measures and a questionnaire measuring iTBS adverse effects and sensations (TMSens_Q).
4. Investigating changes in eating disorder and other related clinical symptoms, measured by scores on clinical symptom questionnaires, visual analogue scales, and BMI, between iTBS and sham groups. This includes estimating treatment effect sizes and standard deviations to inform the sample size calculation for a larger-scale trial.
5. Investigating changes to brain structure and function, measured by structural MRI, ASL, task-negative and task-based functional MRI (fMRI), associated with behavioural and symptom change following iTBS, from baseline to post-treatment (1-month post-randomisation), between iTBS and sham groups.
6. Investigating changes to neurocognitive functioning, measured via performance on tasks involving reinforcement learning, food-related attentional bias, food-related decision making, reward processing, and emotion regulation, from baseline to post-treatment (1-month post-randomisation), between iTBS and sham groups.

As improvements in nutritional and psychological functioning can continue over a period of years, further open follow-ups are planned at 12-months and, if additional funding is obtained, 24-months post-randomisation. The TIARA study found improvements in BMI from baseline to 18-months that were not apparent at 4-months, favouring those allocated to the real rTMS group (Dalton et al., 2020a). These open follow-ups aim to provide longer-term data on the impact of iTBS on AN symptomatology, BMI, mood, and quality of life.

Underpinning hypotheses are based on findings from neuromodulation trials for MDD and our previous studies using rTMS for adults with AN. We hypothesise that, compared to sham iTBS, 20 sessions of real iTBS applied to the left DLPFC will:

1. Be considered by participants as an acceptable, safe, and credible intervention for AN;
2. Reduce AN symptomatology and other related psychopathology;
3. Improve attentional-bias processes, food choice behaviour, and instrumental responding to food cues;
4. Alter the top-down regulation of the DLPFC on limbic areas, for example, the sgACC, ACC and amygdala.

2 | METHODS

This study protocol has been written according to the Standard Protocol Items for Randomised Trials statement (Chan et al., 2013) and the Consolidated Standards of Reporting Trials (CONSORT) statement (Eldridge et al., 2016). Ethical approval for the RaISE trial was obtained from Bradford Leeds Research Ethics Committee (REC ref: 23/YH/0158). The study has been pre-registered on the International Standard Randomised Controlled Trial Number (ISRCTN) registry (registration number: ISRCTN10474541).

2.1 | Trial design

The present study is a multi-centre, longitudinal, triple-blind, two-armed, randomised, sham-controlled trial with a longer-term open follow-up (see Figure 1 for protocol). Consenting participants with AN who meet eligibility criteria will be randomly allocated to receive 20 sessions of real iTBS (treatment group) or sham iTBS

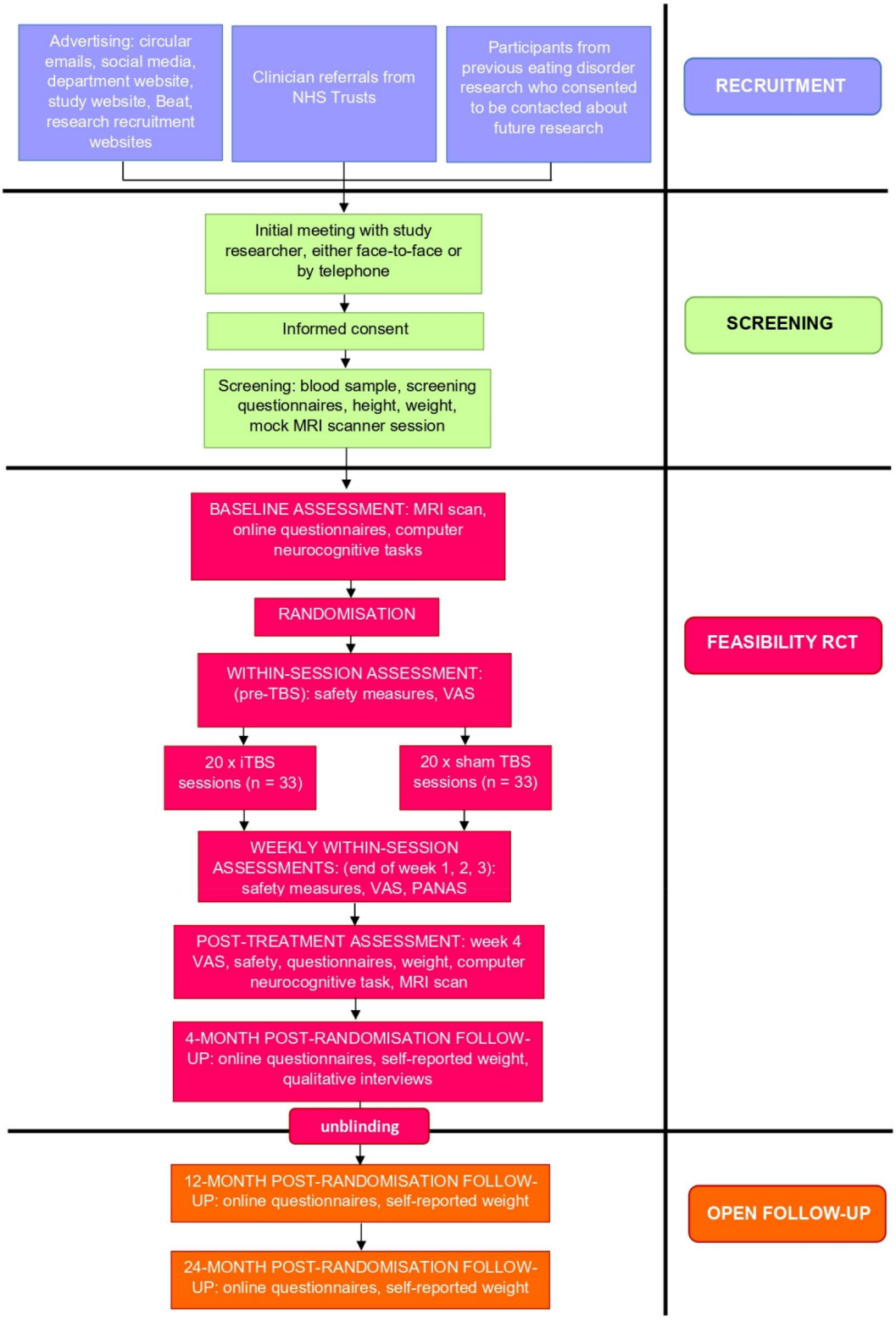

FIGURE 1 Schematic diagram of the RaISE study protocol.

(control group) on consecutive weekdays (over 4-weeks). Participants will be recruited from the community, and iTBS will be delivered in addition to treatment as usual (TAU). Outcomes will be measured at baseline, post-treatment (1-month post-randomisation), and 4-months post-randomisation, prior to unblinding. Open follow-

ups will be conducted at 12- and 24-months post-randomisation, to capture changes that take time to emerge. Selected clinical outcomes will be measured during treatment. Participants in the sham group will be offered the opportunity to receive real iTBS after the 4-month assessment. The protocol is outlined in Figure 1, and Supplementary file 1 gives details of all assessments and time points. The design is closely modelled on our previous trial (TIARA; Dalton et al., 2018) to allow for comparison between the current study and our previous work.

2.2 | Participants

2.2.1 | Eligibility criteria

Participants of any gender will be included if they have a current DSM-5 diagnosis of AN, are aged between 13 and 30 years old, have a BMI of at least 14 kg/m^2 (for participants aged ≥18-years), or 66% of the median BMI for age and gender (for participants aged <18-years), and have completed at least one previous full course of ED treatment (e.g., 6-month course of specialist outpatient therapy, specialist day- or in-patient treatment for refeeding). Participants aged <16-years must have informed consent from parent(s)/guardian(s) and must assent to participation themselves. We will recruit participants up to age 30, expanding on definitions of emerging adulthood and considering the pattern of AN onset and period of increased risk (Solmi et al., 2022), as well as that brain maturation continues until the mid-to-late twenties (Riedel et al., 2022).

People will be excluded if they have a BMI below 14 kg/m^2 or are below 66% of the median BMI for age and gender, are currently receiving inpatient treatment, report a diagnosis of epilepsy or history of seizures of any kind, have experienced severe head injury, have major comorbid psychiatric disorders or symptoms (e.g., acute suicidality) needing treatment in their own right, are on a dose of psychotropic medication that has not been stable for ≥14 days, or have metallic implants anywhere in the body. In addition, we will exclude those that are deemed medically unstable by their clinician (e.g., with major electrolyte imbalance or on a weight loss trajectory) or require immediate inpatient treatment (RCPsych, 2022). Participation of those on a stable dose of any medication that is known to reduce seizure threshold significantly will be assessed on a case-by-case basis, in line with up-to-date safety guidelines (Rossi et al., 2021). Finally, those who have previously received TMS treatment will be excluded to preserve blinding.

2.2.2 | Recruitment and screening

Participants will be recruited from the Eating Disorder Services at the South London and Maudsley NHS Foundation Trust, South West London and St Georges Mental Health NHS Trust and Central and North West London NHS Foundation Trust. Additional centres may be added as needed. Potential participants will be identified by their treating clinical teams. If these participants agree to be contacted, the researcher will send study information materials before any screening procedures occur.

Participants will also be recruited through relevant websites (Beat, UK Eating Disorders Association, King's College London (KCL) research recruitment webpage, edifyresearch.co.uk, etc.), and social media platforms (e.g., Twitter, Instagram, etc.). Individuals who have previously taken part in research at the KCL Centre for Research in Eating and Weight Disorders and have consented to be informed of relevant future studies may also be contacted. Potential participants will receive study information and be screened for eligibility. Eligible participants will provide informed written consent or assent for enrolment into the study (see Supplementary file 2). We have also co-developed a participant recruitment video with young people with lived experience of eating disorders (available at edifyresearch.co.uk), to provide information about iTBS as an intervention and support recruitment.

Screening procedures will include measurements of height and weight, routine blood tests (including electrolytes), the Eating Disorder Diagnostic Scale (EDDS), the TMS Safety Screening Questionnaire (Keel et al., 2001), an MRI safety screen questionnaire developed at King's College London and a short inclusion/exclusion screen specific to this study, including assessment of medical and psychiatric history, and medication dosage and stability.

2.3 | Treatment arms

2.3.1 | Commonalities between groups

All participants will receive 20 real or sham iTBS sessions over 20 consecutive weekdays. These sessions will last approximately 15–20 min, including preparation time, ~4 min of iTBS, and questionnaire administration. Throughout the study, participants can access or continue TAU as their treatment team recommends. TAU will range from GP care to specialist eating disorder care (outpatient, home- or day-treatment).

2.3.2 | Preparation for iTBS sessions

Participants in both groups will undergo a structural MRI scan to locate and deliver neuronavigated real or sham iTBS to the left DLPFC (using Brainsight™). To determine the intensity of iTBS stimulation, participants' resting motor threshold (RMT) will be assessed weekly using the motor-evoked potential method (MEPM) during the 20 real or sham iTBS sessions. RMT is established by determining the minimum stimulator output intensity required to obtain five out of ten motor-evoked potentials greater than 50 μV.

2.3.3 | TBS sessions

A Magstim Rapid device (Magstim®) and Magstim D70-mm air-cooled real or sham coil will be used to administer real or sham iTBS. Participants will watch a film clip consisting of palatable foods whilst receiving real or sham iTBS, as our research group has done in previous studies using rTMS in AN (Dalton et al., 2018), to activate disorder-relevant neural pathways to propagate and prolong iTBS-induced changes in the brain (see Schutter et al., 2023 for state dependency review). Participants allocated to receive 20 sessions of real iTBS will be given a triplet of 50 Hz bursts, repeated at 5 Hz, 2 s on and 8 s off (600 pulses per session) for a total duration of 3 min and 9 s, delivered to the left DLPFC (MNI coordinates: $x = -46$, $y = 45$, $z = 32$) (Dalton et al., 2018). The sham stimulation will be delivered using the same parameters as real iTBS, however, a sham coil will be used (see Section 2.6 for randomisation procedure).

2.3.4 | Safety monitoring

All procedures and parameters are in accordance with current safety and application guidelines for TMS (Rossi et al., 2021). A case record form for each trial participant will be kept to monitor session attendance and protocol violations. In addition, the TMSens_Q (Giustiniani et al., 2022) will be administered every session to measure unintended effects (e.g., sensations, side effects, adverse events). In the event of side effects (e.g., headache) participants will not be withdrawn, but will be able to discontinue iTBS treatment if they wish. iTBS will be halted if the participant experiences a serious adverse event (e.g., seizure), if their BMI falls below 14 kg/m^2 or 66% of the median BMI for age and gender, or if any indicators of serious medical risk emerge. iTBS sessions will only be restarted if it is deemed safe to continue by a medical professional. Additional safety measures include weekly monitoring of participants' weight, blood pressure (sitting and standing), and heart rate, to assess for substantial bradycardia, severe hypotension or major postural drop (RCPsych, 2022). Routine blood tests (i.e., full blood count, urea and electrolytes, and liver and renal function tests) will also be conducted at the start and mid-way through the treatment, or more frequently if clinically indicated. If major abnormalities in the blood sample are present, participation will be paused until medical stability is confirmed by a doctor. If instability persists, the individual would not be able to participate for safety reasons. For the adverse event monitoring and reporting protocol, see Supplementary file 3.

2.4 | Outcome measures

2.4.1 | Screening measures

Participants will complete the following assessments:

- Measurements of weight and height
- Eating Disorder Diagnostic Scale (EDDS; Stice et al., 2000): to confirm AN diagnosis.
- MRI Safety Screen: to ensure participant safety for undergoing an MRI scan.
- TMS Safety Screen (Keel et al., 2001): to check for contraindications to iTBS.
- Safety physical observations: blood pressure, heart rate, and routine blood tests.

2.4.2 | Clinical outcomes

A broad range of outcome measures are included to help determine those that are most sensitive to detecting a treatment effect.

During the RCT:

- ED-related measures: BMI (measured and self-reported), Eating Disorder Examination Questionnaire (EDE-Q; Fairburn & Beglin, 2008), and the Drive for Muscularity, Body Image subscale (McCreary et al., 2004) will be completed pre- and post- real or sham iTBS, as well as at 4-months post-randomisation follow-up.
- Mood and emotion regulation measures: Patient Health Questionnaire-8 (PHQ-8; Kroenke et al., 2009), Positive and Negative Affect Schedule (PANAS; Watson et al., 1988), Profile of Mood States (McNair et al., 1971), and Difficulties in Emotion Regulation

Scale (Bjureberg et al., 2016) will be completed pre- and post- real or sham iTBS, as well as at 4-month follow-up. The PANAS will be completed weekly during the 20-sessions to track mood symptoms with more precision.

- Other symptomatology will be measured by questionnaires including the Generalised Anxiety Disorder-7 (Spitzer et al., 2006), Psychological Outcome Profiles (Ashworth et al., 2004), and Obsessive Compulsive Inventory—Child Version (Foa et al., 2010). These will be completed pre- and post- real or sham iTBS, as well as at 4-month follow-up.
- Other questionnaires including the Work and Social Adjustment Scale, Youth Version (WSAS-Y; Jassi et al., 2020) and the UCLA Loneliness Scale (Russell et al., 1980), will be completed pre- and post- real or sham iTBS, as well as at 4-month follow-up. In addition, the Amsterdam Resting State Questionnaire (Diaz et al., 2013), to capture the cognitive state of participants during resting state fMRI, will be completed at pre- and post- real or sham iTBS. The Substance Use Risk Profile Scale (Woicik et al., 2009) will be completed once, at baseline.
- Visual analogue scales, consisting of a 10 cm line upon which a participant will indicate the degree of endorsement of a particular feeling, from 'not at all' to 'extremely'. These will assess core AN features, mood, anxiety, and motivation and readiness to change. These will be completed at each sham or real iTBS session, as well as pre- and post-iTBS, and at 4-month follow-up.
- Offline neurocognitive tasks assessing attentional biases to food using a visual probe task (Werthmann et al., 2019), food choice behaviour (Steinglass et al., 2015), information processing biases for positive and negative facial expressions using a Go No-Go task (Bland et al., 2016), and the influence of Pavlovian conditioned food-related stimuli on instrumental learning (Vogel et al., 2020) will be completed at pre- and post- real or sham iTBS.

During the open follow-up:

The 12- and 24-month open follow-up assessments will include self-reported BMI, the EDE-Q, the WSAS-Y and the PHQ-8.

2.4.3 | Treatment expectations, tolerability and acceptability

Treatment expectations, tolerability, and acceptability of iTBS will be assessed by the TMSens_Q and thematic analysis of semi-structured qualitative interviews with participants, exploring initial expectations, perceived positives and negatives, and suggestions for improvement. Qualitative interviews will be scheduled after unblinding at 4-months, and the topic guide will be modelled closely after that from TIARA (Dalton et al., 2022), adapted for a younger population.

2.4.4 | Service utilisation outcomes

Utilisation of treatments and services outside of the iTBS will be assessed via self-report at baseline, weekly throughout the intervention, and at 4-month follow-up. This will also be reported at 12- and 24-month open follow-ups.

2.4.5 | Neuroimaging outcomes

MRI measures at baseline and post-treatment include:

- Structural MRI for neuronavigation of the iTBS coil and for assessing whole-brain structural changes following iTBS using T1 weighted images acquired using an enhanced fast gradient echo 3-dimensional pulse sequence (TR: 7.3 ms; TE: 3.0 ms; number of slides: 196; voxel size: 1.2 × 1.05 × 1.05 mm; FOV: 270 mm; inversion time: 400 ms).
- fMRI involving paradigms assessing inhibitory motor control in a Stop Signal Task (SST), reward processing in a Monetary Incentive Delay (MID) Task, and emotional experiences during movie-watching using an echo planar imaging (EPI) sequence for all tasks (TR: 2200 ms; TE: 30 ms; number of slices: 40; slice thickness: 3 mm, slice gap: 3.3 mm, number of volumes: SST = 349, MID = 191, FOV: 240, flip angle: 75°, matrix: 64 × 64 mm). Previous research has suggested alterations in inhibitory control, reward processing, and emotion processing and regulation are implicated in the development and maintenance of AN, associated with altered DLPFC-limbic connectivity. These paradigms have been selected with this in mind to allow exploration of neurocognitive correlates of iTBS response.
- Resting-state fMRI to study neural networks at rest (TR: 2500 ms, echo times: 12, 28. 44 ms, flip angle: 80°, FOV: 240, voxel size: 4 × 4 × 3 mm; 32 axial sections collected with continuous descending acquisition and 1-mm interslice gap).
- ASL to obtain a quantitative measure of cerebral blood flow at rest (TR: 5,135 ms, TE: 11.1 ms, number of slices: 56, slice thickness: 3 mm, slice gap: 3 mm, FOV: 240, flip angle: 111°, matrix: 512 × 8 mm).

2.5 | Sample size

As this is a feasibility study, no a priori sample size calculation is required. We have chosen a target sample size of $n = 60$, similar to or exceeding that of other feasibility trials in this area (e.g Dalton et al., 2018; Dhami et al., 2019). To aid us in collecting longer-term follow-up data, we will aim to recruit a total sample size of $N = 66$ to account for an assumed attrition to follow-up rate, a = 0.0625 (as in Dalton et al., 2018) and after applying an attrition correction factor of 1/(1–a), we will need a sample size of $N = 66$, that is, 33 participants per intervention arm.

2.6 | Randomisation

Generation and implementation of the randomisation sequence will be conducted independently from the trial team by the KCL Clinical Trials Unit (CTU). Once the participant has been recruited, provided informed consent, and completed the baseline assessment, the researcher will enter the participant ID and stratification details into the web-based CTU system. Participants will then be allocated to one of the two trial arms using a restricted stratified randomisation algorithm, stratifying by prognostic factors (subtype of AN—restricting or binge-purge; and previous hospitalisation—yes or no).

2.7 | Blinding

Participants and the researchers conducting assessments and delivering iTBS will be blinded to treatment allocation. The KCL CTU will inform an independent researcher of the participant allocations, who will change the sham or treatment coil. To assess allocation concealment, participants and researchers will be asked to guess treatment allocation at the end of iTBS treatment and to indicate how confident they are in this guess. Participants will be debriefed and unblinded to group allocation upon completion of the 4-month follow-up. At this timepoint, participants allocated to the sham condition will be offered real iTBS following the same protocol described above.

2.8 | Statistical analyses

2.8.1 | Feasibility

Our primary feasibility outcome is retention, the proportion of participants retained up to 4-months out of the total number of participants randomised. Other feasibility metrics include recruitment rate, quality, completeness, and variability in the data, and acceptability (measured by sessions of real or sham iTBS completed out of 20). Estimation of effect sizes and standard deviations will inform sample size calculations for future trials. The safety of iTBS for young people with AN will be assessed via tracking TMS adverse events and sensations (measured by the TMSens_Q), allowing us to conduct two-way ANOVAs to establish whether there is a significant difference in adverse events and sensations between those in the sham and active groups.

2.8.2 | Clinical outcomes

Analyses will follow the intent-to-treat principle. Descriptive statistical analyses and graphical methods will be used to determine quality, completeness, and variability in outcome measures. For each outcome measure, the iTBS effect size will be the difference in outcome data between those in the sham and those in the real iTBS groups.

Group differences will be estimated using linear mixed-effects regression models, controlling for baseline levels of each outcome. This is with the aim of informing outcome measure selection and sample size calculations for a future large-scale RCT. To investigate the relationship between changes in neurocognitive function, neural changes shown by neuroimaging methods, and clinical symptom improvement measured via BMI and symptom questionnaires, multiple regression models will be used.

2.8.3 | Service utilisation data

Descriptive statistical analyses will be used to examine participants' additional treatment utilisation.

2.8.4 | Qualitative data

Interviews will be recorded, transcribed, and analysed using thematic analysis (Clarke & Braun, 2021).

2.8.5 | Neuroimaging analysis

- Structural MRI: Voxel-based morphometry (VBM) analyses will be conducted to evaluate any morphological changes resulting from 20 sessions of iTBS.
- ASL: We will use whole-brain voxel-wise and regions of interest (ROI) analyses to test for an effect of real

iTBS on rCBF. ROIs will be defined a priori, based on the literature and previous findings (Dalton et al., 2021) and will include the sgACC and rostral ACC, left DLPFC, and the amygdala.

- Resting-state fMRI: Hypothesis-led seed-based connectivity (sgACC and rostral ACC, and the amygdala) analyses will be conducted to assess interactions between treatment group (real vs. sham iTBS) and timepoint (pre- or post-iTBS).

For whole-brain analyses, results will be considered significant if they survive familywise error correction based on cluster-extent ($pFWE_C<0.05$), using a cluster-forming threshold of $p < 0.001$.

2.9 | Patient and public involvement

This study is part of a larger programme of research (EDIFY, which was co-developed with seven young people with lived experience of eating disorders (EDs)). This panel emphasised the needs of young people with persistent EDs that have not benefitted from first-line treatments, as such, the RaISE trial aims to improve treatment options for these young people. With EDIFY youth advisors, we have co-developed a participant information and recruitment video, with accessible information to ensure young people have a good understanding of what iTBS involves before taking part. The video was reviewed along with the study design by the NIHR Maudsley BRC adolescent advisory group. The video and overall study protocol has been endorsed by these advisors. EDIFY youth advisors (IM, KM, LZ) reviewed this paper and provided critical feedback to shape the final manuscript.

3 | DISCUSSION

Treatment outcomes for those with AN who have not benefitted from first-line psychological therapies are poor, with no psychological intervention demonstrating superiority in treating this group (Solmi et al., 2021). This, along with the limited evidence supporting pharmacotherapy for AN (Cassioli et al., 2020), and advances in our understanding of the neural underpinnings of AN (e.g., Frank et al., 2019; Kaye et al., 2009; O'Hara et al., 2015), show the importance of advancing the evidence base for the use of therapeutic neuromodulation in AN.

This paper outlines the protocol for a triple-blind, sham-controlled feasibility RCT of iTBS for young people with persistent AN. The RaISE trial will be the first investigation of iTBS treatment for AN, and will provide important insights into the feasibility of a large-scale trial, while also exploring the neural underpinnings and mechanisms of clinical improvement in neuromodulation for AN. The open longer-term follow-up period will capture changes (e.g., weight) that take time to emerge, and provide essential data on the longer-term outcomes of neuromodulation, which are often missing in trials of therapeutic neuromodulation (Rachid, 2018). The protocol adheres to current safety recommendations (Rossi et al., 2021) and is consistent with previous research using rTMS in AN. We will include a variety of measures to identify the most appropriate tools to detect iTBS-induced changes across AN-related symptoms, behaviours and neurocognition, to inform future larger-scale trials.

Several practical and logistical issues may pose a challenge to the timely completion of this trial and to the feasibility of iTBS as a treatment for young people with persistent AN in general. Such concerns include the duration of iTBS sessions, and whether participants may find the travel time to perceived treatment quality ratio unfavourable. This may impact retention of participants, especially with consideration to the likely educational and/or organisational demands present in young peoples' lives. However, in our previous multi-session RCT of rTMS in adults with AN, the retention rate was very high (94%) (Dalton et al., 2018). We will similarly reimburse participants for assessments, and retention, as our primary feasibility outcome, will be closely monitored. Where possible, we will be flexible with iTBS session and assessment scheduling, to fit with participants' work or educational commitments.

Though iTBS is safe and tolerable for children and adolescents (Elmaghraby et al., 2022), discomfort during iTBS may be a barrier to feasibility, especially considering our sample is younger than in previous investigations using rTMS for AN. We will continually assess tolerability, via the TMSens_Q, and at the 4-months follow-up with qualitative interviews.

4 | CONCLUSIONS

Novel treatments for AN are lacking for those who have not recovered with current options. Conventional rTMS has demonstrated short- and longer-term efficacy in AN (Dalton et al., 2018, 2020a), and non-inferiority of iTBS has been established in the MDD literature (Blumberger et al., 2018). This two-armed, sham-controlled RCT will assess the feasibility of iTBS for young people with AN, and provide short- and longer-term data on treatment efficacy, and the neural and neurocognitive biomarkers and correlates of treatment response. Hopefully, the

findings will facilitate the development of available treatments for those with persistent AN.

AUTHOR CONTRIBUTIONS

Ulrike Schmidt and Helen Sharpe developed the main conceptual ideas for the EDIFY programme. Ulrike Schmidt, Helen Sharpe, Iain C. Campbell, Başak İnce, Lucy Gallop and Amelia Hemmings contributed to the design of the study. Lucy Gallop and Amelia Hemmings co-wrote the first draft of the manuscript, and all other authors provided critical feedback and approved the final version before submission.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

Not applicable—this manuscript does not contain any data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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