ISRCTN10474541 https://doi.org/10.1186/ISRCTN10474541

Intermittent theta burst stimulation for young people with persistent anorexia nervosa

Submission date
25/05/2023

Recruitment status
No longer recruiting

Registration date
01/06/2023

Overall study status
Ongoing

Last Edited
05/02/2025

Condition category
Mental and Behavioural Disorders

[X] Prospectively registered
[X] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol
Background and study aims
Anorexia Nervosa (AN) is a serious disorder with often devastating consequences. For people with AN who do not respond to first-line psychological therapies, and/or have a longer illness duration, there are currently no specific superior treatments associated with positive longer-term outcomes. Research suggests that self-regulatory ability is weakened in a range of neuropsychiatric disorders, including AN. This could be a consequence of developmental dysfunction in frontostriatal circuits (neural pathways in brain). High-frequency repetitive transcranial stimulation (rTMS) can improve self-regulatory control and also symptoms in disorders that have a frontostriatal dysfunction. The first multi-session RCT of rTMS for people with AN demonstrated short and longer-term efficacy. This study employs a non-inferior protocol (Intermittent theta burst stimulation, iTBS) with a shorter stimulation period compared to classical high-frequency rTMS.

The aim of this study is to assess the feasibility of iTBS as an adjunct to treatment for young people with AN, by collecting data on recruitment, retention, acceptability, and tolerability, with retention of participants our primary outcome. We will also explore changes in AN and related clinical symptoms, BMI, quality of life, neurocognitive processes, and neural structure and function. Effect size estimates will inform the sample size calculation for a future larger-scale trial.

Who can participate?
Participants of any gender will be eligible if they have a current diagnosis of AN, are aged between 13-30 years old, have a BMI of >14kg/m² (for participants >18 years old) or 66% of the median BMI for age and gender (for participants <18 years old), and have completed at least one previous course of eating disorder treatment. Participants aged <16 years must have informed consent from parents or guardians.

What does the study involve?
Participation involves having two brain scans (before and after the intervention) and 20-sessions of real or sham (placebo) iTBS. In order to detect the effects of iTBS, not all participants will receive real iTBS, that is, half of the participants will receive a sham (placebo) iTBS stimulation. This will be random allocation and participants will not be aware of which (real or sham)

stimulation they receive, however, will be informed upon completion of the 3-month follow-up assessment. Participants will also be required to complete a number of questionnaires, and neurocognitive tasks (brain puzzles) before and after the 20-sessions of real or sham iTBS. We will also collect blood samples for safety at baseline and mid-way through the 20-sessions.

What are the possible benefits and risks of participating?
The most common side effect of iTBS is a mild discomfort in the scalp beneath the magnetic coil, but some people also referred to a mild headache (easily treated with simple analgesic drugs). The magnetic coil makes loud clicks during treatment that are not loud enough to harm hearing, but patients will be asked to wear earplugs as a precaution. An inbuilt safety mechanism in the machine keeps the coil at a safe temperature. Although iTBS is regarded as a safe intervention, the most serious side effect reported, though very rare, is a seizure (with an incidence of 0.02%). The rTMS Safety Screen will be done before iTBS and a daily evaluation of unintended effects (e.g., sensory sensations) with the iTBS will also be done with the TMS adverse events and associated sensations questionnaire. There are no risks associated with the administration of the neurocognitive tests and other questionnaires or MRI scans. Participants who receive real TBS may experience short and longer-term improvements in mood and eating disorder symptoms.

Where is the study run from?
Participants will be recruited from the outpatients eating disorder service at the South London and Maudsley NHS Foundation Trust and South West London St Georges Mental Health NHS Foundation Trust, and via advertisements on charity, research participation and social media websites. The study will be conducted at the Institute of Psychiatry, Psychology and Neuroscience, London (UK).

When is the study starting and how long is it expected to run for?
May 2023 to February 2026

Who is funding the study?
Funding to conduct the trial is provided by the Medical Research Council/Arts and Humanities Research Council/Economic and Social Research Council Adolescence, Mental Health and the Developing Mind initiative as part of the EDIFY programme (grant number MR/W002418/1).

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
318129

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 318129, CPMS 57132

Study information

Scientific Title
Randomised controlled feasibility trial of intermittent theta burst stimulation (iTBS) for young people with persistent anorexia nervosa: RaISE

Acronym
RaISE

Study objectives
The primary aim of this study is to investigate the feasibility of iTBS as a treatment for young people with anorexia nervosa, with a view to acquire information to develop a large-scale randomised controlled trial of therapeutic TBS in this population.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Multi-centre longitudinal triple-blind two-armed randomized sham-controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Anorexia nervosa

Interventions
66 participants will be randomised to receive real or sham iTBS in a parallel group, triple-blind study design.

Intermittent theta burst stimulation (iTBS) consists of a coil that is held by the researcher over the head of the participant which delivers pulses of magnetic field with a preselected frequency (50Hz in this study) and strength (determined individually as 80% of the motor threshhold). An individual's motor threshold will be determined by finding the minimum stimulus output to evoke 5 out of 10 motor evoked potentials greater than 50 microvolts. The target site for stimulation, the left DLPFC will be located using the brain scans acquired from structural MRI. Neuronavigation software called Brainsight will be used to locate the area from the scan uploaded.

Participants allocated to receive 20 sessions of real iTBS will be given a triplet of 50Hz bursts, repeated at 5Hz, 2 seconds on and 8 seconds off (600 pulses per session) for a total duration of 3 minutes and 9 seconds, delivered to the left DLPFC (MNI coordinates: x = -38, y = 44, z = 26). The sham stimulation will be delivered using the same parameters as real iTBS, however, a sham coil will be used. This protocol is similar to those used in other studies and are within those recommended for safe use.

Randomisation
Generation and implementation of the randomisation sequence will be conducted independently from the trial team by the King's clinical trials unit (CTU). After a participant has been recruited, provided informed consent, and completed the baseline assessment, the researcher will enter participant ID and stratification details (previous hospitalisation: Y/N; AN subtype: restrictive or binge-purge) into the web-based CTU system. Participants will then be allocated to either real or sham iTBS groups using a restricted stratified randomisation algorithm. An independent researcher will be informed by the CTU of the participant allocation, and be responsible for changing the sham or treatment coils before each participant.

Intervention Type
Procedure/Surgery

Primary outcome(s)
Retention of participants in the study measured via percentage of participants retained out of total number of participants randomised, at 4-months.

Key secondary outcome(s))
1. Acceptability, measured via adherence to 20-sessions of iTBS, TMS adverse events and associated sensations questionnaire (administered at each daily iTBS session), and qualitative interviews scheduled after unblinding at 4-month follow-up.
2. Credibility of iTBS, measured via qualitative interviews scheduled after unblinding at 4-month follow up.
3. Recruitment rates measured via number of participants recruited per site per month.
4. Attendance rates measured by sessions of real or sham iTBS completed out of 20, at the end of treatment (1-month).
5. Determining the best instruments for measuring outcomes in a full trial by examining the

quality, completeness, and variability in the data measured throughout the trial (at baseline, daily during the 20-sessions, at post-treatment, 4-month follow-up)
6. Estimating the treatment effect sizes and standard deviations for clinical outcome measures (measured at baseline, daily during the 20-sessions, at post-treatment, 4-month follow-up) to inform the sample size calculation for a larger-scale trial.
7. Safety of TBS for young people, via cardiac measures collected weekly throughout the 4-week trial period, and a questionnaire measuring TMS adverse effects and associated sensations administered daily at each iTBS session.
8. Eating disorder symptoms (measured at baseline, daily during the 20-sessions, at post-treatment, 4-month follow-up, and again at open-longer term follow-ups at 12- and 24-months post-randomisation).
9. Other related clinical symptoms, measured by scores on clinical symptom questionnaires and visual analogue scales (measured at baseline, daily during the 20-sessions, at post-treatment, 4-month follow-up, and again at open-longer term follow-ups at 12- and 24-months post-randomisation).
10. Changes to brain structure and function, measured by structural MRI, arterial spin labelling, task-negative and task-based functional MRI (fMRI), associated with behavioural and symptom change following TBS, from baseline to post-treatment (1-month), between iTBS and sham groups.
11. Changes to neurocognitive functioning, measured via performance on tasks involving reinforcement learning, food-related attentional bias, food-related decision making, temporal discounting, and emotion regulation, from baseline to post-treatment (1-month), between iTBS and sham groups.

Completion date
28/02/2026

Eligibility

Key inclusion criteria
1. Participants of any gender between the ages of 13 and 30 years
2. Living in the community (either in outpatient or day patient treatment, or with no current treatment for their AN).
3. BMI 14 kg/m² or above (for participants aged 18 years or above) or over 66% of the median BMI for age and gender (for participants under the age of 18)
4. Current Diagnostic and Statistical Manual-5 (DSM-5) diagnosis of AN-restricting type (AN-R) or AN-binge/purging type (AN-BP).
5. Must have completed at least one adequate previous course of eating disorder treatment (e.g., one 6-month course of specialist outpatient therapy, specialist day-care or in-patient treatment for refeeding)
6. Participants under the age of 16 years must have informed consent from parent(s)/guardian(s) in addition to giving assent themselves
7. Those currently receiving treatment must have approval from treating eating disorder clinician or GP to participate. For those not currently receiving treatment, their GPs will be notified.
8. Must use and understand English as a language for everyday conversation

Participant type(s)
Patient

Healthy volunteers allowed

No

Age group
Mixed

Lower age limit
13 years

Upper age limit
30 years

Sex
All

Key exclusion criteria
1. Having a history of head or eye injury
2. Having a current inpatient admission for AN treatment
3. Having a history of a neurological disease including previous seizures of any kind
4. Having metallic implants anywhere in the head or body
5. Being on a dose of any psychotropic medication that has not been stable for at least 14 days prior to participation in the study- Taking anti-convulsive medication
6. Pregnancy or suspected pregnancy in female participants
7. Having a current other major psychiatric disorder (e.g., major depressive disorder, bipolar illness, substance dependence, psychosis) needing treatment in its own right
8. Excessive alcohol (scoring >5 on the AUDIT-C) and/or cigarette consumption (>15 cigarettes per day)
9. Severe abnormalities in the screening clinical blood sample
10. An rTMS safety questionnaire and an MRI safety questionnaire will also be administered and if deemed not safe to deliver rTMS or undergo MRI scanning, people will be excluded on this basis.

Date of first enrolment
30/08/2023

Date of final enrolment
30/11/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Institute of psychiatry, psychology and neuroscience
16 De Crespigny Park

London
United Kingdom
SE5 8AB

Sponsor information

Organisation
King's College London

ROR
https://ror.org/0220mzb33

Funder(s)

Funder type
Government

Funder Name
UK Research and Innovation

Alternative Name(s)
UKRI

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		01/02/2024	05/02/2025	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes