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Repetitive transcranial magnetic stimulation (rTMS) and neuroimaging in anorexia nervosa

Submission date
22/07/2015

Recruitment status
No longer recruiting

Registration date
23/07/2015

Overall study status
Completed

Last Edited
18/08/2023

Condition category
Mental and Behavioural Disorders

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Anorexia nervosa (AN) is a disabling and deadly disorder. After about 3-5 years, AN can be considered as enduring and difficult to change. Most adults with AN have an enduring form of the illness, and only 10-30% of adults treated with best available treatments make a full recovery. Treatment innovations are urgently needed. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation method that has been used successfully to treat psychiatric disorders, such as depression. rTMS appears to increase the brain's ability to form new nerve connections, and hence it is thought to be of value in chronic or treatment-resistant mental disorders. We have shown that a single session of rTMS can temporarily reduce eating disorder symptoms. We have also treated five cases of enduring and treatment-resistant AN with 20 sessions of rTMS, with all individuals showing sustained improvements in eating disorder symptoms and mood. The proposed study is a randomised control feasibility trial investigating rTMS as an adjunct to treatment for AN. The study will compare the effect of 20 sessions of real vs. sham (placebo) rTMS over a 4 week period in adults with severe and enduring AN, using a number of neuroimaging measures to explore the neural mechanisms underlying the treatment effect. This is a clinical trial of a potential new treatment for AN. As such, although we hope there will be, we do not know whether there will be any benefits to participants in terms of symptom improvement. In the long-term, this research will help us develop improved treatments for AN.

Who can participate?
Right handed adults (aged at least 18) with a BMI between 14 and 18.5 kg/m2 and diagnosed with AN.

What does the study involve?
Participants are allocated at random to receive 20 sessions of either real rTMS or a sham version of this treatment in addition to their usual treatment (~1 hr per weekday for 4 weeks). We measure weight, eating disorder symptoms, mood and other outcomes before, during and after treatment and 3-months later to assess treatment success. With the help of two brain scans (one before and one after treatment) we assess how rTMS impacts on brain processes thought to

underlie the symptoms of AN. Finally, we also ask participants about their experience of this treatment. Participants assigned to the sham condition are offered real rTMS after they have completed their involvement in the study.

What are the possible benefits and risks of participating?
Participants may find the procedures slightly uncomfortable. In that case, participants are free to withdraw from the study at any time without the need to justify their decision. If a participant decides to withdraw from the study, this will not affect the treatment they receive. The most common side effect of rTMS is mild discomfort in the head beneath the magnetic coil. Some people suffer a mild headache, which is treatable with simple painkillers such as paracetamol. The most serious side effect, but a very rare one (less than 1% likelihood in healthy people), is an epileptic seizure. None of our previous participants have experienced a seizure during rTMS. We will complete a safety questionnaire to exclude circumstances that would be associated with an increased risk for a seizure. We will also monitor participants' blood electrolyte levels before and during the study, as altered electrolyte levels may increase seizure risk. rTMS might induce a slight change to the structure and/or function of the brain (e.g. hormone levels), and participants may experience a temporary difference in their thoughts and/or mood. We will be checking this by examining changes in their performance on computerised tasks and by comparing brain scans taken before and after receiving rTMS treatment. Lastly, although rTMS is used widely in research and clinical settings, there is still the possibility of some, as yet unknown, side effects of the intervention. We will frequently assess any discomfort participants may experience throughout their involvement in the trial. MRI scanning is a safe scanning technique. Prior to the scan, participants will complete a screening questionnaire to make sure it is safe for them to go in the scanner. There is the possibility that an abnormality will be found in participants' brain scan. These are called incidental findings and are found in about 4% of people who have a scan done. A limited assessment of the MRI scans will be performed by a specialist – identification of a major abnormality that requires action will be reported to the participants' doctor (as specified on their MRI consent form). The study investigators will be informed that the participant's GP has been contacted, but will not be told the exact nature of the abnormality. In such an event, we will have to withdraw the participant from the study to ensure their safety. Participants will be compensated £10 for their time on the days of their pre-, post-treatment and follow-up testing sessions. They will also be compensated up to £5 for their travel expenses on all study and treatment days.

Where is the study run from?
Maudsley Hospital, London and Institute of Psychiatry, Psychology and Neuroscience, King's College London (UK)

When is the study starting and how long is it expected to run for?
August 2015 to June 2017

Who is funding the study?
This study is funded by the National Institute of Health Research and the South London and Maudsley NHS Foundation Trust Biomedical Research Centre.

Who is the main contact?
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Contact information

Type(s)
Public

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Protocol serial number
19152

Study information

Scientific Title
TIARA (repetitive Transcranial magnetic stimulation and neuroImaging in AnoRexia nervosA): a sham-controlled randomised feasibility study of repetitive transcranial magnetic stimulation (rTMS) as an adjunct to treatment as usual (TAU) in adults with severe and enduring anorexia nervosa (SE-AN)

Acronym
TIARA

Study objectives
This is a feasibility trial. As such the overarching aim of this project is to establish the utility of neuronavigated high frequency repetitive transcranial magnetic stimulation (rTMS) delivered to the left dorsolateral prefrontal cortex (DLPFC) as a potential adjunct to treatment as usual (TAU) for adults who suffer from severe and enduring anorexia nervosa (SEED-AN) and to acquire key information to inform the development of a large-scale randomised sham-controlled trial (RCT). In parallel neural correlates of this treatment will be explored.
The specific objectives of the proposed feasibility study are to:
1. Establish the feasibility of conducting a large-scale RCT of rTMS in SEED-AN patients by assessing recruitment, attendance, and retention rates
2. Determine the best instruments for measuring outcomes in a full trial by examining the quality, completeness, and variability in the data
3. Estimate the treatment effect sizes and standard deviations for outcome measures to inform the sample size calculation for a large-scale RCT
4. Evaluate whether the treatment is operating as it is designed by analysing process measures, such as within session visual analogue scales of key eating disorder symptoms

5. Determine whether patients with SEED-AN view rTMS as acceptable and credible
6. Obtain information about patients' willingness to undergo random allocation to real or sham rTMS

Tentative underpinning hypotheses are as follows: Based on pilot studies previously conducted by our group in eating disorder patients it is predicted that compared to sham-treatment, 20 sessions of high-frequency rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) treatment will:
1. Reduce AN symptomatology, encourage a change in weight/BMI and improve related psychopathology (e.g. depression, anxiety and stress)
2. Improve self-regulatory abilities (assessed using neuropsychological computer tasks, e.g., temporal discounting, stop signal task), complemented by a change in task-based neural activity and connectivity between the DLPFC and the inhibitory control network (i.e., right inferior frontal gyrus, pre supplementary motor area)
3. Alter neural activity in the DLPFC at rest (e.g., blood flow) and during the fMRI tasks, which will be correlated with symptom improvement

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee London - City Road & Hampstead, 17/03/2015, ref: 15/LO/0196

Study design
Randomized; Interventional; Design type: Treatment

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Topic: Mental Health; Subtopic: Eating disorders; Disease: Eating disorders

Interventions
Participants in this trial will receive 20 sessions of real or sham rTMS, with sessions taking place 5 times per week (e.g., Monday-Friday) for 4 weeks. Through mapping of the First Dorsal Interosseous (FDI) muscle, the intensity of the rTMS will be acquired by obtaining the individuals motor threshold (MT) which represents membrane-related excitability of cortical axons. To ensure safety and efficacy, the MT will be assessed weekly for each participant during their 20 rTMS treatment sessions. Using the Motor Evoked Potential Method (MEPM), the MT is established by determining the minimum stimulator output intensity required to obtain 5 out of 10 motor evoked potentials (MEP) greater than 50μV. Based on this measurement, twenty sessions of high frequency rTMS (10Hz) at 110% of the individual's MT, consisting of twenty 5seconds trains with 55seconds inter-train intervals will be delivered to the left DLPFC. We propose to use the individual structural MRI scans acquired from the pre-treatment MRI session in order to locate the left DLPFC, identified by co-ordinates x =-45 y =45 z=30 [56]. A Magstim Rapid device (Magstim®, UK) and Magstim D70mm air-cooled real/sham coil will be used to administer real and sham rTMS. All of the aforementioned protocol, including establishing each individuals MT will be identical between groups. The sham stimulation will be given at the same

location and frequency as the real rTMS however a sham coil will be used. The sham coil makes the same noise as the real coil but does not deliver a magnetic field. All of these procedures and parameters are in accordance with the current safety and application guidelines for rTMS.

Throughout the study participants will be able to access/continue treatment as usual (TAU) for their AN as recommended by their treating team.

Intervention Type
Device

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
-

Primary outcome(s)
Clinical and cognitive outcomes
1. BMI is measured with height and weight at baseline, weekly during treatment, at post-treatment, and at 3-month follow-up
2. Eating disorder symptomatology is measured with the Eating Disorders Examination Questionnaire (EDE-Q), Fear of Food Measure (FOFM), and Self-Starvation Scale at baseline, post-treatment, and 3-month follow-up. The FOFM and a short version of the EDE-Q will also be completed weekly during treatment
3. Current eating disorder experience are measured with visual analogue scales before and after each daily rTMS session
4. Other psychiatric symptomatology is measured with the Depression, Anxiety and Stress Scales (DASS), Positive and Negative Affect Schedule, Profile of Mood States, and Intolerance of Uncertainty Scale at baseline, post-treatment, and 3-month follow-up. The DASS is also completed weekly during treatment
5. Inhibitory control is measured with a proactive inhibition task at baseline, post-treatment, and 3-month follow-up
6. Attentional bias to food measured with the Visual Probe Task at baseline and post-treatment
7. Food choice behaviour is measured with the Food Choice Task at baseline and post-treatment
8. Impulsivity/compulsivity are measured with the Delaying Gratification Inventory, Barratt Impulsiveness Scale, and Obsessive-Compulsive Inventory at baseline, post-treatment, and 3-month follow-up
9. Cognitive control over emotions is measured with the Emotion Regulation Questionnaire at baseline, post-treatment, and 3-month follow-up.
10. Cognitive flexibility is measured with the Cognitive Flexibility Scale at baseline, post-treatment, and 3-month follow-up
11. Self-efficacy is measured with the Eating Disorder Recovery Self-Efficacy Questionnaire at baseline, post-treatment, and 3-month follow-up.
12. Quality of life is measured with the EuroQol Quality of Life Scale at baseline and 3-month follow-up
13. Illness impact is measured with the Clinical Impairment Assessment at baseline and 3-month follow-up
14. Treatment expectations, tolerability and acceptability of rTMS are measured with visual analogue scales weekly during treatment and with thematic analysis of semi-structured

interviews at 3-month follow-up
15. Service utilisation of treatments and services other than rTMS is measured with a self-report version of the Clinical Service Receipt Inventory at baseline and 3-month follow-up

Neuroimaging outcomes
1. Whole-brain structural changes are measured at baseline and post-treatment
2. Functional changes (involving paradigms assessing inhibitory motor control in a Stop Signal Task and motivational control in a temporal discounting task) are measured at baseline and post-treatment
3. Changes in cerebral blood flow are measured at baseline and post-treatment

Key secondary outcome(s))
There are no secondary outcome measures

Completion date
31/03/2017

Eligibility

Key inclusion criteria
1. Male and female participants who are aged 18 or over
2. BMI between 14 and 18.5 kg/m2
3. Right-handed
4. Current DSM-V diagnosis of AN-Restricting type (AN-R) or AN-Binge/purging type (AN-BP) and an illness duration of 3 years or more
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. Must have approval from treating Eating Disorders clinician or GP to participate

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
34

Key exclusion criteria

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

Date of first enrolment
01/08/2015

Date of final enrolment
31/12/2016

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
King's College London
Institute of Psychiatry, Psychology and Neuroscience
16 De Crespigny Park
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Study participating centre
South London and Maudsley NHS Foundation Trust
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Sponsor information

Organisation
King's College London

ROR
https://ror.org/0220mzb33

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	16/07/2018	23/10/2019	Yes	No

Results article	Participant experiences	09/07/2021	12/07/2021	Yes	No
Results article		12/02/2022	14/02/2022	Yes	No
Results article	protocol	28/01/2021	18/08/2023	Yes	No
Protocol article		03/12/2015		Yes	No
HRA research summary			28/06/2023	No	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