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A double-blind randomised controlled trial of repetitive Transcranial Magnetic Stimulation (rTMS) in the treatment of persistent auditory hallucinations in schizophrenia

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No longer recruiting

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12/09/2003

Overall study status
Completed

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27/10/2016

Condition category
Mental and Behavioural Disorders

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

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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ClinicalTrials.gov number

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N0071109120

Study information

Scientific Title
A double-blind randomised controlled trial of repetitive Transcranial Magnetic Stimulation (rTMS) in the treatment of persistent auditory hallucinations in schizophrenia

Study objectives
We hypothesise that rTMS is an effective treatment for schizophrenic auditory hallucinations. We predict that the administration of rTMS, in addition to current medication, will produce a significant improvement in the level of auditory hallucinations in subjects with schizophrenia who are experiencing persistent auditory hallucinations.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Not specified

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Mental and Behavioural Disorders: Schizophrenia

Interventions
Participants:
Hoffman et al (2000) found a change of four from baseline in the hallucination score with standard deviation six, comparing sham and active treatments. To detect this will require about 26 patients in each cell for 90% power and 5% significance. To compare left rTMS against control, assuming that right rTMS is ineffective will then yield 52 patients per arm. To compare any active treatment with sham will yield 78 patients in the active arm and 26 in the control. This 3:1 ratio will reduce the power slightly to give 80% confidence in detecting a change of 4.5 units of hallucination score.

The statistical power calculation requires a total of 104 subjects to enable the study to detect the predicted outcomes. All Sheffield general psychiatry consultant teams will be contacted and invited to refer from their in-patient and out-patient caseload.

A drop-out rate of 10% is predicted. We will, therefore, recruit 20% more subjects than is required by the power calculation (126 in total) in order to take account of this and any compliance problems. We aim to recruit patients at a rate of seven per month, which will give a total of 126 patients over 18 months. In Sheffield, between April 1999-April 2000, there were 475 patients with schizophrenia aged more than 18 years who had recorded clinical contact with mental health services. The planned recruitment is compatible with this number of potential subjects, and is particularly facilitated by the closeness of contact between such patients and mental health services. Divergence from target rates by month 12 will prompt possible extension of trial to other local Trusts, e.g. Rotherham and Doncaster, which will expand the total population to in excess of 1.1 million and give an estimated total of 950 potential subjects.

Interventions:
The study will be a factorial, double-blind, randomised controlled trial. Throughout the trial, all subjects will continue to receive standard care from their responsible consultant psychiatrist. No restrictions will apply to the changes that may be made to standard care during the study.

Subjects will be randomised into one of the four arms of the factorial design. Randomisation will proceed in a stratified manner, matching the groups for age, sex, handedness and severity of auditory hallucinations. Subjects will be blind to their experimental allocation.

The procedure in each of the four arms will be administered to the subjects once daily for ten consecutive working days. Prior to commencing treatment each subject in an active rTMS arm will have their Motor Threshold (MT) determined by the application of single pulses of TMS over the motor cortex. All rTMS will be administered by a doctor in the ECT suite or comparable environment.

The four arms of the trial and the associated interventions are:
A. Left only: rTMS at a frequency of 1 Hz and amplitude 100% MT applied to left temporal cortex for 20 minutes.
B. Right only: rTMS at a frequency of 1 Hz and amplitude 100% MT applied to right temporal cortex for 20 minutes.
C. Left and right: rTMS at a frequency of 1 Hz and amplitude 100% MT applied to left temporal cortex for 10 minutes followed by right temporal cortex for 10 minutes.
D. Sham (placebo) stimulation, using a modified coil, which produces no magnetic field but has an acoustic signature similar to that of an active coil, applied to left temporal cortex for 20 minutes.

The parameters (frequency, intensity and duration) of clinically useful rTMS have not yet been firmly established. The range of parameters described in the literature is diverse. The parameters in this study are based upon those found to be effective in reducing auditory hallucinations by Hoffman et al. The study parameters are all within the limits recommended by the international safety guidelines for rTMS.

Outcome measures:
A second (or more) psychiatrist(s) who is blind to their experimental allocation will assess the level of auditory hallucinations experienced by all subjects. A description of the measurements to be made, and a timetable for these, is given below. Prior to commencing the main study, a

pilot period will allow reliability to be checked and established. Each subject is assessed over a 25 week cycle. rTMS sessions take place in the weeks designated 0 and +1.

Analyses:
The data obtained will be subject to a primary intention to treat analysis. A secondary per-protocol analysis will also be undertaken. The two main comparisons in the primary analysis will be:
1. Left rTMS versus control (A+C versus B+D).
2. Active rTMS versus sham (A+B+C versus D).

A repeated measures analysis with a random effects model will be used to test the significance of the between groups comparisons. Before and after within group comparisons will also be made and tested.

In addition to these continuous measures, outcomes will also be analysed in dichotomous terms. The main a priori dichotomous outcome will be defined as a 50% reduction in baseline auditory hallucinations as measured by the visual analogue scale. Rational post-hoc analysis of dichotomous outcomes will be permitted.

Estimates of the true magnitude of differences in the comparisons, and of the relative event rate for a positive outcome, will be calculated using confidence intervals for the differences between means and for proportions.

Intervention Type
Other

Phase
Not Specified

Primary outcome measure
1. Change from baseline in auditory hallucinations score according to a visual analogue measure of current intensity, as used by Hoffman et al (2000).
2. Change from baseline in the auditory hallucinations sub-scale score from SAPS as a measure of frequency of auditory hallucinations over the past week.

Secondary outcome measures
1. Complete SAPS and Scale for the Assessment of Negative Symptoms (SANS) scores as a measure of change in total schizophrenic symptoms.
2. 17-item Hamilton Depression Rating Scale (HAMD) as a measure of change in mood. The HAMD is the most commonly used measure for treatment trials of depression, and has been widely applied to this end in reported trials using rTMS.
3. Changes in physical, psychological and social functioning are assessed with the Short Form 36 Health Survey Questionnaire (SF-36).
4. Medication type and levels are recorded at all assessment points.
5. rTMS side effects are recorded at all assessment points.
6. Neuropsychological and audiometric tests are carried out before and after the treatment phase of the trial.
7. Patient satisfaction will be assessed after the treatment phase.
8. 'Blindness' of subjects and assessors will be assessed after the treatment phase.

Overall study start date

01/12/2001

Completion date
30/11/2004

Eligibility

Key inclusion criteria
1. Male and female, aged 18 to 65
2. Subjects will fulfil the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) diagnostic criteria for schizophrenia.
3. They will also continue to experience auditory hallucinations defined as a score of more than two on the auditory hallucinations sub-scale of the Scale for the Assessment of Positive Symptoms (SAPS) for more than six weeks despite standard clinical treatment by a psychiatric team.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
65 Years

Sex
Both

Target number of participants
126

Key exclusion criteria
1. Organic brain disorder
2. Previous documented unconsciousness
3. Unstable coronary heart disease
4. Contra-indications to rTMS, e.g. history of fits, recent cerebro-vascular accident, history of epileptic seizures, metal implants, cardiac pacemakers

Date of first enrolment
01/12/2001

Date of final enrolment
30/11/2004

Locations

Countries of recruitment

England

United Kingdom

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Funder(s)

Funder type
Government

Funder Name
Sheffield Health and Social Research Consortium (UK)

Results and Publications

Publication and dissemination plan

Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration