ISRCTN16758036 https://doi.org/10.1186/ISRCTN16758036

Trial of a non-invasive stimulation method to treat visual hallucinations in people with macular degeneration

Submission date
22/01/2019

Recruitment status
No longer recruiting

Registration date
29/01/2019

Overall study status
Completed

Last Edited
26/01/2023

Condition category
Eye Diseases

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

Plain English summary of protocol

Background and study aims
Charles Bonnet Syndrome (CBS) occurs in patients who experience recurrent visual hallucinations (VH) secondary to visual impairment, such as macular degeneration, and in the absence of psychiatric illness. It is estimated that up to fifty percent of patients with macular degeneration experience visual hallucinations and up to one-third of those consider the experience to be distressing and disruptive to day-to-day life. Currently, there are no effective treatments for CBS. Drug treatments can include medications known as cholinesterase inhibitors, anticonvulsants and antipsychotics, which have been found to offer little benefit and often have severe side effects. Therefore, there is a distinct need to develop new and effective treatments. Earlier research has suggested that visual hallucinations experienced by people with eye disease are the result of increased activity (or excitability) in the visual cortex, the seeing part of the brain. It is believed that as the visual cortex is deprived of sensory information sent from the eyes due to visual impairment, this causes spontaneous and independent activity to occur in the visual system, resulting in the formation of visual hallucinations. Transcranial direct current stimulation (tDCS) is an established, non-invasive (i.e. applied from outside the body) and well-tolerated technique which can alter the activity or excitability levels of the brain using a weak electrical current. This change in the brain has also been found to be sustained, particularly when repeated tDCS is applied. tDCS involves the attachment of two electrode pads to the scalp which produce a negative pole (anode) which increases activity in the brain, and a positive pole (cathode) which diminishes activity. As CBS is understood to be the result of increased excitability of the visual cortex, the aim of this study is to test whether applying cathodal stimulation to this area will result in a reduction in this activity and reduce visual hallucinations, thus providing direct evidence that increased excitation or activity in the visual system is responsible for visual hallucinations in CBS.

Who can participate?
Patients aged over with 18 Charles Bonnet Syndrome

What does the study involve?
The study involves two phases. In the first phase, CBS patients who experience continuous or

highly frequent visual hallucinations (multiple hallucinations each day) receive active cathodal tDCS over the visual cortex. Before stimulation, electroencephalography (EEG), a technique which measures brain activity, is used to indicate which areas of the visual cortex are demonstrating increased excitability and are the best target for cathodal stimulation. In order to determine the best stimulation settings needed to cause an effective reduction in visual hallucinations, the researchers alter the current strengths, electrode positions, and lengths of stimulation. Participants then provide immediate feedback as to whether stimulation has caused an alteration in their visual hallucinations. In Phase II, a second group of CBS patients are randomly allocated to receive a course of active tDCS (using the optimal settings found during phase I) and a course of placebo (dummy) tDCS over several days. Following a four week period, participants return and receive the opposite treatment (i.e. if they received placebo tDCS in their first week, they receive active tDCS in their second). Before stimulation, patients undergo assessments of their visual hallucination severity, which are then followed up immediately after treatment ends to see if stimulation has produced any benefits. In addition, further techniques are used to look at activity levels in the brain before and after stimulation and the effect of stimulation on vision. These include transcranial magnetic stimulation (TMS), a technique which activates the visual part of the brain using a special magnetic device against the back of the head, magnetic resonance imaging (MRI), which collects detailed images of the brain using a magnetic resonance scanner, and EEG to measure brain signals as in Phase I. Patients also have their eyesight assessed both before and after tDCS to determine whether stimulation has an effect on this. Each technique is performed on the patient's first visit and then again following the end of the treatment for both the active and placebo weeks, to determine the effects of tDCS on the brain and to confirm whether visual hallucinations in CBS patients are the result of increased activity in the visual part of the brain.

What are the possible benefits and risks of participating?
This study is trying to find out whether treatment with direct current stimulation reduces visual hallucinations. This will help to develop better treatments. Thousands of people worldwide have undergone direct current stimulation without experiencing any major side effects. Some people experience a tingling sensation with the stimulation, and sometimes a temporary reddening of the skin on the head under the sites where pads are placed during direct current stimulation. Very occasionally, some people may experience a short-lasting headache which can be treated with over-the-counter painkillers. Rarely, some people report feeling sick, have problems sleeping or difficulties with their concentration, although these symptoms are usually short-lived. Sometimes people are also allergic to the electrode pads, but the researchers will check whether participants have had any problems with skin allergies before entering the study. Participants also undergo magnetic stimulation on two occasions, some rare cases have reported some discomfort during stimulation and, occasionally, headaches, but these are also easily treated with painkillers. In extremely rare cases magnetic stimulation has been reported to cause a seizure, but this only seems to have happened in people with a history of seizures. The researchers will check whether participants are at risk of having a seizure or epilepsy before entering the study. EEG is a very safe technique and very few people report any side effects. However, some people may experience temporary redness under electrode pads on the scalp or mild discomfort during electrode set-up. On rare occasions people may experience a headache from the EEG cap or, like with direct current stimulation, may have an allergic reaction to electrode pads or gel. Similarly, magnetic resonance imaging (MRI) is very safe, there is no radiation known to be associated with the scan and the scan is not painful. Some people may feel claustrophobic in the scanner or may experience some discomfort from lying still or flat for a long period of time. Participants are able to leave the scanner at any time they wish and the radiographer performing the scan will communicate with them throughout the scan to check

that they are comfortable. Certain medications may exclude people from participating in this study, but this will be assessed before they take part. During participation, participants continue taking their normal medication and are not asked to make any changes.

Where is the study run from?
Newcastle University (UK)

When is the study starting and how long is it expected to run for?
April 2017 to June 2020

Who is funding the study?
1. Macular Society
2. Fight for Sight UK
3. Thomas Pocklington Trust
4. Randerson Foundation
5. NIHR Newcastle University BRC
6. Northumberland, Tyne and Wear NHS Foundation Trust

Who is the main contact?
1. Mrs Kirsty Olsen
2. Ms Kat Da-Silva Morgan

Contact information

Type(s)
Public

Contact name
Mrs Kirsty Olsen

Contact details
Campus for Ageing & Vitality
3rd Floor
Biomedical Research Building
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United Kingdom
NE4 5PL

Type(s)
Scientific

Contact name
Ms Kat Da-Silva Morgan

Contact details
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3rd Floor
Biomedical Research Building
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United Kingdom
NE4 5PL

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
220721

Study information

Scientific Title
Treating VISual hallucinations in people with MACular degeneration: a non-invasive stimulation study (VISMAC)

Acronym
VISMAC

Study objectives
1. To determine, mechanistically, whether tDCS can be used to reduce the frequency, duration, severity and emotional impact of visual hallucinations in patients with Charles Bonnet Syndrome
2. To improve understanding of the underlying mechanisms involved in visual hallucinations in Charles Bonnet Syndrome

Ethics approval required
Old ethics approval format

Ethics approval(s)
North East - Tyne & Wear South Research Ethics Committee, Room 001, Jarrow Business Centre, Rolling Mill Road, Jarrow, Tyne & Wear, NE32 3DT, Tel: +44 (0)207 104 8124, Email: nrescommittee.northeast-tyneandwearsouth@nhs.net, 07/06/2017, ref: 17/NE/0131

Study design
Interventional single-centre study

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Home

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Charles Bonnet Syndrome

Interventions
Randomisation, blinding & unblinding
Randomised lists will be generated by a researcher/statistician who is independent and not associated with the study and will be contained in a set of sealed opaque envelopes, one of which will be kept in a secured password-protected database accessible only to the independent researcher. The randomisation will be 1:1 allocation to active:placebo tDCS using the online randomisation tool (www.randomization.com).
The tDCS machine will be programmed by an appropriately qualified researcher independent to the study team with patient identifiers and whether they are to receive active or sham stimulation. Thus the technician/experimenter who delivers the tDCS (entering only a coding number into the tDCS machine), the rater, and the patient will be blind to which stimulation is being used. In the event of a serious adverse event during the course of the study, this randomisation code can be broken. Unblinding for data analysis will only be carried out after completion of all data collection, except for the case of examination of the data by any independent data monitoring and/or the ethics committee. On the Day 5 visit for both active and placebo stimulation blocks, the integrity of the blind will be assessed by asking participants and their treatment assessors whether they believed they were receiving the real stimulation or the dummy (placebo) one and why they think this. The treatment assessor will then be asked to record their answers on a separate sheet and prior to asking the participant in order to avoid bias.

Transcranial Direct Current Stimulation (tDCS) involves the application of a weak electrical current (<2mA) between scalp surface electrodes. Participants with CBS will receive one session of active or placebo stimulation each day for four consecutive days. Stimulation will be delivered using a Starstim wireless 8-channel EEG/tCS neurostimulator system (Neuroelectrics, Barcelona, Spain) using 3.41cm2 electrodes soaked in conductive gel. Electrodes will be placed on the basis of the international 10-20 electrode placement with the cathode placed over the occipital region and the anodal reference electrode will be placed over either a cephalic or non-cephalic region. Electrodes will be held in place using a neoprene cap.

If participants receive active stimulation in their first block, then the second block (after a wash-out period of 4 weeks) will consist of placebo stimulation. Placebo/sham stimulation will be delivered at the same intensity as active tDCS for the first 7-15 seconds (same initial ramping function as active treatment) then will be switched off.

Intervention Type
Procedure/Surgery

Primary outcome measure
The acute benefits of tDCS on visual hallucinations at Day 5 after active stimulation in comparison to placebo. The effect that stimulation has on visual hallucinations will be assessed in terms of duration, severity, frequency and emotional impact of the hallucinations across the four day stimulation period, using the North East Visual Hallucinations Index (NEVHI) adapted for use in CBS patients, and the Neuropsychiatric Inventory (NPI) hallucinations subscale score.

Secondary outcome measures
All measured on day 1 (baseline) and day 5 of the trial. This will happen on both treatment weeks:

1. Visual function including:
1.1. Visual acuity (Freiburg test)
1.2. Contrast sensitivity (Freiburg contrast test)
1.3. Visual field (tangent screen)
1.4. Visual distortion (Amsler chart)
1.5. Higher visual function screening
2. Excitability in the visual cortex measured using the repeat phosphene excitability measure
3. Resting state EEG, including alpha band and gamma activity
4. Visual cortical function and metabolic GABA/glutamate levels

Baseline data collected from EEGs, including alpha and gamma activity, TMS phosphene thresholds, structural, cortical function, and metabolic GABA/glutamate levels, will also be compared between patients with CBS and the control group.

Overall study start date
01/04/2017

Completion date
30/06/2020

Eligibility

Key inclusion criteria
All participants:
1. Age >18, either sex
2. Provision of written informed consent
3. MMSE-blind >24
4. Absence of any concurrent major psychiatric illness (e.g. major depression) or dementia
5. Absence of severe physical illness or co-morbidity that may limit ability to fully participate in study
6. Sufficient English to allow assessment scales and cognitive testing

Charles Bonnet Syndrome:
1. Meet the diagnostic criteria of CBS: Cognitively intact, having complex visual hallucinations (with no hallucinations in other modalities or delusions), full insight into the unreality of these, and presence of eye disease sufficient to cause visual impairment
2. Evidence of persistent and recurrent episodes of visual hallucinations determined to be of stable frequency with the expectation of at least one hallucination per day

Control (eye disease):
1. Presence of eye disease sufficient to cause visual impairment
2. No prior history of visual hallucinations

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
20 patients with CBS

Total final enrolment
43

Key exclusion criteria
All participants:
1. Skin allergies or sensitivities to electrode gels or any significant dermatological/scalp disease
2. Past history of excess alcohol intake
3. Past history of other neurological illness including, but not limited to, stroke, intracerebral pathology, and epilepsy
4. Metal or electronic implants (including pacemakers) which might be affected by strong magnetic fields (occurring in TMS or MR component of the study) or electrical currents (tDCS component)

Charles Bonnet Syndrome:
1. Psychotropic and other medications which may significantly interfere with cognitive testing and tDCS efficacy (including high dose antipsychotics, dopamine agonists, sedative antidepressants, benzodiazepines except when in low dose and used as hypnotics, and centrally acting anticholinergic drugs)
2. Evidence for Lewy body symptoms and signs which may cast doubt on a CBS diagnosis (i.e. REM sleep disorder).

Control (eye disease):
1. Past history of visual hallucinations

Date of first enrolment
01/02/2018

Date of final enrolment
31/03/2020

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Newcastle University
Newcastle upon Tyne
United Kingdom
NE4 5PL

Sponsor information

Organisation
Northumberland Tyne & Wear NHS Trust

Sponsor details
St Nicholas Hospital
Jubilee Road
Gosforth
Newcastle upon Tyne
England
United Kingdom
NE3 3XT

Sponsor type
Hospital/treatment centre

Website
www.ntw.nhs.uk

ROR
https://ror.org/01ajv0n48

Funder(s)

Funder type
Charity

Funder Name
Macular Society

Alternative Name(s)
Macular Disease Society, The Macular Society

Funding Body Type
Government organisation

Funding Body Subtype

Associations and societies (private and public)

Location
United Kingdom

Funder Name
Fight for Sight UK

Alternative Name(s)
Fight for Sight

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name
Thomas Pocklington Trust

Funder Name
Randerson Foundation

Funder Name
NIHR Newcastle University BRC

Funder Name
Northumberland, Tyne and Wear NHS Foundation Trust

Alternative Name(s)

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
It is planned to publish this study in peer review articles and to present data at national and international meetings. Results of the study will also be reported to the Sponsor and Funder, and will be available on their website. All manuscripts, abstracts or other modes of presentation may be reviewed by the Trial Steering Group and/or funder prior to submission. Individuals will not be identified from any study report. No additional documents are/will be available.

Intention to publish date
30/01/2023

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr John-Paul Taylor (John-paul.taylor@ncl.ac.uk). Imaging and clinical phenotypic data. Data available upon request to study chief investigator 24 months after study end. Available for 5 years. All participants consented to share anonymised data.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/12/2022	26/01/2023	Yes	No
HRA research summary			28/06/2023	No	No