ISRCTN52484108 https://doi.org/10.1186/ISRCTN52484108

Assessing visual cortex in candidates for retinal prosthetics

Submission date
07/12/2015

Recruitment status
No longer recruiting

Registration date
04/01/2016

Overall study status
Completed

Last Edited
16/03/2018

Condition category
Eye Diseases

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

Plain English summary of protocol

Background and study aims
Macular degeneration (MD) is the most common cause of vision loss in the western world. It mostly effects the elderly (age-related macular degeneration, or AMD). It involves the gradual damage to a part of the eye called the macula. The macula is a tiny area at the centre of the retina (the layer at the back of the eye which is sensitive to light), which is responsible for central vision (seeing what is directly ahead). Over time, the damage to the macula can lead to central vision becoming distorted or blurry, eventually causing a blank patch in the centre of a person's vision. In most cases, AMD is caused by fatty-protein deposits called drusen collecting under the retina (dry AMD) over a long period of time; currently there is no cure or effective treatment for this type. About 10% of people suffering from AMD have what is known as wet AMD (or neovascular AMD). In wet AMD, the macula becomes damaged and new blood vessels start to grow behind the retina. These blood vessels are generally very weak and prone to leakage, causing the macula to swell and vision to deteriorate very quickly. This form can be treated to improve vision and to prevent further damage. MD is particularly devastating because it is central vision that is most critical for daily activities such as reading, driving, recognising faces, watching television, etc. New therapies are being developed to treat and restore vision in patients with dry MD and other eye diseases. One approach is to implant an electronic chip in the eye to replace the function of the cells damaged by the disease. The Argus® II Retinal Prosthesis System, developed by Second Sight Medical Products, Inc., is the most successful example of this technology to date. NHS ethical approval has recently been granted to test the Argus® II implant in patients with MD in a small study run by Professor Paulo Stanga at the Manchester Royal Eye Hospital. A large proportion of the parts of the brain involved in vision (the 'visual cortex') receive information from the central retina of the eye. MD therefore effectively cuts off these brain areas from visual input. When patients have been partially or fully blind for many years, these 'unused' parts of the brain may begin to take on new roles and process other information, or they may even degenerate and lose their ability to function altogether. Most research on vision restoration has focused on treating the eye. However, since visual perception ultimately takes place in the brain, the visual cortex must be able cope with inputs from the eye once they are restored. With participants from the study in Manchester, magnetic resonance imaging (MRI) will be used to assess the structure and function of the visual cortex of the brain in MD patients before and after implantation with the Argus® II Retinal Prosthesis System. It will lay the groundwork for a larger study aimed at answering the following

questions, which have both clinical and scientific significance:
1. Which measures of brain structure and function prior to retinal prosthetic implantation best predict successful restoration of vision in patients with macular degeneration?
2. Do neural changes occur in brain structure and function when visual inputs are reintroduced?
3. Which measures of brain structure and function after implantation best predict the success of retinal prosthetic implants in restoring sight?
It is hoped that answering these questions will contribute to the development of tools to help clinicians predict the success of retinal prosthetics and other treatments aimed at restoring peoples sight. In addition, researchers hope to gain a better understanding of brain plasticity (changes to the brain) and the mechanisms underlying recovery of sight in adults with MD.

Who can participate?
Participants from the Argus II Retinal Prosthesis System Dry AMD Feasibility Study in Manchester (https://clinicaltrials.gov/show/NCT02227498).

What does the study involve?
All participants undergo MRI scanning to look at and compare two regions of the brain. The first is the “lesion projection zone” of the brain, which is the part of the brain that normally receives input from the damaged part of the eye. The second is the “intact projection zone”, which is the part of the brain that receives input from the undamaged parts of the eye. The researchers also use MRI to look at the effects of the surgical implantation with the retinal prosthesis. The participants undergo two sessions, once before their retinal implantation and once 12 months after it has taken place.

What are the possible benefits and risks of participating?
There is no guarantee of any direct benefit to participants in this study. Potential harmful risks will be avoided by screening participants to ensure that MRI will not harm them. In addition, all MRI scanning procedures will follow the implant manufacturer’s guidelines. Some people might feel claustrophobic or discomfort in confined spaces such as the MRI scanner. If so, these participants will not be included in the study. Some participants (particularly those who have not had an MRI scan before) may find it uncomfortable to remain as still as possible for an extended period of time. Foam cushions are used to minimise any discomfort and help support the head in a static position. As the MRI scanner operates at high noise levels, all participants are given ear plugs and plenty of cushioned head support to maintain noise levels within safe limits. A two-way intercom is used by the MRI operator to communicate with the participant at regular, frequent intervals (every few minutes). Participants will also be given an emergency squeeze ball to indicate if they feel at uncomfortable at any time either during a scan or between scans. This will stop the scanner immediately and the MRI operator will enter the scanning chamber to retrieve the participant.

Where is the study run from?
University of York (UK)

When is the study starting and how long is it expected to run for?
February 2015 to February 2016

Who is funding the study?
Centre for Chronic Diseases and Disorders (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Study information

Scientific Title
Assessing visual cortex in candidates for retinal prosthetics: a single-centre feasibility /observational study

Study objectives
1. Which measures of brain structure and function best predict successful restoration of vision in patients with macular degeneration implanted with retinal prosthetic devices?
2. Do neural changes occur in brain structure and function when visual inputs are reintroduced after retinal prosthetic implantation?

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. IRAS (Integrated Research Application System), 11/03/2015, ref: 171426
2. University of York, Department of Psychology, 22/07/2015, ref: P1277

Study design
Single-centre feasibility/observational study

Primary study design
Observational

Study type(s)

Treatment

Health condition(s) or problem(s) studied
Age-related macular degeneration (AMD)

Interventions
The purpose of the pilot study is to develop quantitative methods to assess brain structure and function in participants with macular degeneration in order to predict the success and measure the effects of vision restoration.

We will recruit participants from a linked pilot study led by our collaborator Prof Paulo Stanga at the Manchester Royal Eye Hospita (https://clinicaltrials.gov/show/NCT02227498), the first clinical trial to implant the Argus® II Retinal Prosthesis System in patients with macular degeneration. As Prof Stanga's pilot study is limited to five patients, our study will also include no more than five participants. Therefore, our participants will meet the inclusion and exclusion criteria for Prof Stanga's study as well as meeting the additional requirements for magnetic resonance imaging (MRI) safety and compatibility. We have chosen to use MRI as it is a well-established, safe and relatively non-invasive method to measure brain structure and function in human participants both in the clinic and in research, and we (the investigators) have extensive experience in using MRI in similar patient groups. In addition, the manufacturers of the Argus® II (Second Sight Medical Products, Inc.,Sylmar, CA, USA) have tested the retinal implant in the MRI scanner with the procedures we will be using and have deemed it safe for participants. All MRI scans will follow the safety guidelines of the manufacturer for the Argus® II and will be performed with the retinal implant switched OFF.

All participants in our study will undergo all procedures (with their informed consent). Therefore, they will serve as their own controls (a within-subjects design). Comparisons will be made across two independent variables, each of which will have two levels. One independent variable will be the region of interest (location in the visual cortex of the brain), consisting of:
1. The LPZ or 'lesion projection zone', the part of the brain that normally receives input from the damaged part of the eye
2. The IPZ, or 'intact projection zone', the part of the brain that receives input from unaffected parts of the eye, which will serve as a within-subject control region.
The other independent variable will measure the effects of treatment, consisting of measurements made:
1. Before surgical implantation
2. After surgical implantation with the retinal prosthesis.

The null hypotheses are:
1. No difference in MRI measurements between the two regions of interest (LPZ vs. IPZ)
2. Measurements in the two regions of interest will not change with treatment.
Regions of interest will be chosen based solely on anatomical features, not using any of MRI measurements that form the dependent variables in the study. Regions of interest will be independently selected and verified by a second researcher.

Dependent variables will consist of the following measures:
1. Structural MRI: We will characterise the anatomical properties of visual cortex using several standard structural MR imaging sequences. Quantitative measurements will include grey and white matter volume, grey matter thickness and myelination levels. Based on previous research we hypothesise that both grey and white matter measures will be significantly smaller in the LPZ (from damaged retina) compared to the control region, the IPZ (control region) before

treatment. We hypothesise that these measures will increase in the LPZ once inputs are restored by retinal implant treatment.
2. Functional MRI (fMRI): We will test functional properties of visual cortex by acquiring fMRI (T2*-weighted) scans to measure blood oxygenation level dependent (BOLD) brain responses to visual stimuli (images).

Visual stimuli will include:
1. Large checkerboard stimuli for identifying visual areas (retinotopic mapping)
2. Natural images (e.g. faces) presented while participants perform a simple 'one-back' task (press a response button whenever they see two identical images in a row). A large ‘X’ target that is visible both before and after implantation will help patients fixate and keep eyes steady during scanning. The level of brain activity (strength of the BOLD response) will be compared in the regions of interest before and after implantation. Based on previous research, we hypothesise that activity in the LPZ will occur only in MD patients when performing a task. We hypothesise that task-related activity in the LPZ will diminish after treatment, in agreement with results from normally sighted participants.
3. Magnetic resonance spectroscopy: Lack of input to the LPZ may result in long-term neural suppression of activity within this region, which may not resolve when inputs return. Magnetic resonance spectroscopy (MRS) will also be performed to assess relative levels of the inhibitory neurotransmitter GABA within the LPZ relative to that within the IPZ before implantation. Although MRS is a form of MRI, it has not been explicitly tested with the Argus® II implant and will thus only be performed before implantation. GABA levels within the LPZ vs. IPZ will be used as a prognostic measure to predict the success of vision restoration as determined by the clinical tests outlined above.

The study will require participants to visit the University of York on two occasions - once before retinal implantation and once about 12 months after implantation.

Intervention Type
Device

Primary outcome(s)
The purpose of this study is the feasibility for conducting a larger study in the future. To determine this, the following primary outcomes will be evaluated:
1. Participant's tolerance, comfort and safety during each measure (to be noted down in writing by researcher during debriefing at the end of each visit)
2. Which neural measures are most reliable and least affected by implant artifacts and other noise sources? (by evaluating each neural measure outside of the main regions of interest)
3. Which neural measures are most predictive of successful vision restoration following retinal implantation? (by correlation with visual improvement as assessed by Prof Stanga with clinical vision tests)
4. Which neural measures are most effective for assessing visual cortical changes following retinal implantation? (based on outcome of secondary, scientific measures)

Neural measures refer to the amount of brain activation measured with MRI in response to visual stimulation. Measured before retinal implantation and once about 12 months after implantation.

Key secondary outcome(s))
Secondary outcome measures will be the scientific assessment of neural characteristics of visual cortex within each participant before and after retinal implantation.

1. Structural measures will include grey and white matter volume, cortical thickness and myelination fraction (macromolecular tissue volume), which will gauge the potential changes in myelinated input to primary visual cortex.
2. Functional measures will include the blood oxygenation level dependent (BOLD) response level to simple and complex stimuli, and the position of stimulation within the visual field that yields the highest response (retinotopic mapping), and the level of the inhibitory neurotransmitter GABA.
3. To control for variability across participants and sessions, a ratio will be used to compare each the neural measures at the lesion projection zone (part of the brain receiving inputs from the macular, lesioned retina) and the intact projection zone (part of the brain receiving inputs from the peripheral, intact retina) within each participant and each session (before and after treatment).

Measured before retinal implantation and once about 12 months after implantation.

Completion date
23/02/2016

Eligibility

Key inclusion criteria
Participants for our study will be drawn only from participants in the Argus II Retinal Prosthesis System Dry AMD Feasibility Study led by Prof Paulo Stanga in Manchester (https://clinicaltrials.gov/show/NCT02227498). Therefore, participants must meet the inclusion criteria specified for this study. Broadly, this includes adult participants with the 'dry' form of macular degeneration without other eye problems that would preclude retinal prosthetic implantation.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Senior

Sex
All

Key exclusion criteria
Participants will be subject to the exclusion criteria outlined in the linked study 'Argus II Retinal Prosthesis System Dry AMD Feasibility Study Protocol' (https://clinicaltrials.gov/show/NCT02227498).

In addition, participants with contraindications for magnetic resonance imaging (MRI) will not be included in this study. Contraindications for MRI include the following:
1. A cardiac pacemaker
2. Operations involving implantation of metal or other implants that may not be MRI compatible
3. A programmable hydrocephalus shunt
4. Cochlear implant
5. Fixed dental braces

6. Injuries involving metal fragments or shrapnel
7. Metal piercings that cannot be removed
8. Certain medicinal patches incompatible with MRI
9. Close relatives of the investigators
10. Epilepsy/seizures
11. Severe claustrophobia or discomfort maintaining a supine position in the MRI scanner

Date of first enrolment
23/02/2015

Date of final enrolment
23/02/2016

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of York
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Sponsor information

Organisation
University of York

ROR
https://ror.org/04m01e293

Funder(s)

Funder type
University/education

Funder Name

Centre for Chronic Diseases and Disorders

Alternative Name(s)
C2D2

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Stored in repository