ISRCTN51601294 https://doi.org/10.1186/ISRCTN51601294

Finding brain signals that might guide the delivery of deep brain stimulation

Submission date	Recruitment status	[ ] Prospectively registered
27/01/2020	Suspended	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
31/01/2020	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
09/04/2020	Nervous System Diseases	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Parkinson's disease (PD) is, unfortunately, a common, disabling, progressive condition characterised by severe problems with movement for which medical treatment in the longer term is unsatisfactory. Deep brain stimulation (DBS) is a treatment which directly stimulates the nerves affected inside the brain to help overcome the difficulties with action. However, this treatment is currently limited by costs, side effects and a partial effect. This may be due to the fact that current DBS stimulates in a manner that is constant and independent of a patients underlying condition as reflected in their brainwave activity. This study aims to improve DBS treatment by testing whether one can adjust DBS stimulation in real time using analyses of brain signals recorded from DBS electrodes. The researchers have already identified abnormal brain signals that are associated with worsening of Parkinson's disease but only in the period immediately after surgery.

Who can participate?
Patients aged 18 to 80 with Parkinson's disease, essential tremor or dystonia who have completed stage 1 of a two-stage surgery for DBS as therapy for their movement disorder

What does the study involve?
The study will be carried out prior to their second operation (stimulator implantation) and will be carried out during a single inpatient stay. The researchers will firstly analyse DBS brain signals one month after implantation when swelling is reduced and signals are more representative. Secondly, the researchers will test patients using standard stimulation settings versus a responsive mode in which stimulation settings are adjusted according to the levels of abnormal signals that are present. It is hoped that these experiments with discover the most representative signals in chronically implanted Parkinsonian patients and show that these signals can be used to drive responsive stimulation and improve power consumption.

What are the possible benefits and risks of participating?
There is no direct benefit to research participants other than contributing to research progress in the field. Participants will not receive remuneration or travel expenses. Risks to participants entering this trial are minimal. The recording and rating techniques are all safe and carry no risks. The techniques have been used in many previous UK and international studies. Stimulation of

the DBS electrodes can cause side effects, so the researchers will only deliver stimulation in the form and range used clinically, taking care to always remain below the threshold for side-effects. Side-effects are possible tingling, muscle cramps and slurring of speech. These only last as long as the stimulation is applied at relatively high intensity, and disappear with weaker intensities. They may equally occur during the standard clinical use of DBS for therapy. If there are side-effects due to stimulation the stimulation intensity will be reduced so that these side-effects are no longer experienced. As the researchers will be connecting to (disposable) leads that link to the DBS electrodes there is no increase in infection risk has been seen due to recordings in patients with externalised DBS leads. Participants who are on medication for their motor symptoms may omit their medication on the day of the study and can resume it immediately after the study ends. The participant may only experience a temporary and reversible exacerbation of their symptoms, similar to forgetting a dose.

Where is the study run from?
John Radcliffe Hospital (UK)

When is the study starting and how long is it expected to run for?
July 2019 to July 2024

Who is funding the study?
1. Medical Research Council (UK)
2. National Institute for Health Research (NIHR) (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Integrated Research Application System (IRAS)
271953

Central Portfolio Management System (CPMS)
42210

Study information

Scientific Title
An investigation into the chronic neurophysiological biomarkers of Parkinson's disease (PD) and their application to closed loop deep brain stimulation (DBS)

Study objectives
Parkinson’s disease (PD) is, unfortunately, a common, disabling, progressive condition characterised by severe problems with movement for which medical treatment in the longer term is unsatisfactory. Deep brain stimulation (DBS) is a treatment which directly stimulates the nerves affected inside the brain to help overcome the difficulties with action. However, this treatment is currently limited by costs, side effects and a partial effect. This may be due to the fact that current DBS stimulates in a manner that is constant and independent of a patients underlying condition as reflected in their brainwave activity. This project aims to improve DBS treatment by testing whether one can adjust DBS stimulation in real time using analyses of brain signals recorded from DBS electrodes. The researchers have already identified abnormal brain signals that are associated with worsening of Parkinson’s disease but only in the immediate post-operative period.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 03/05/2011, South Central - Oxford C Research Ethics Committee (Level 3, Block B, Whitefriars Building, Lewins Mead, Bristol, BS1 2NT, UK; Tel: +44 (0)207 104 8241, 0207 104 8041; Email: nrescommittee.southcentral-oxfordc@nhs.net), ref: 11/SC/0100

Primary study design
Interventional

Study design
Non-randomised; Interventional; Design type: Treatment, Device, Physical, Surgery

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Parkinson's disease

Interventions
The study will take place either in the Neurosciences Ward or the Charles Wolfson clinical research facility (one floor below the ward) in the John Radcliffe University Hospital according to the patient's preference. The above represents only one study site.

Patients will be enrolled who are undergoing surgery for deep brain stimulation as therapy for a movement disorder. Surgery will be performed purely on clinical grounds. Some of such patients have a staged surgery with stage 1 consisting of electrode implantation and stage 2 consisting

of the connection of the electrodes to a subcutaneous stimulator and battery unit. This staging is performed for clinical reasons (such as testing of stimulation effects prior to committing to implantation of an expensive stimulator and battery unit) or service reasons (such as maximising the efficiency of surgical operating time). It is these patients who the researchers hope to study. Patients will be studied over up to two days between stage 1 and stage 2, which are usually separated by 4-7 days. On each study day, the patient will undergo recording and testing that may last up to 4 hours. Thus the patient is only asked to volunteer for one or two days study and no other visits are required. Whether the study takes one or two days depends on the patients' preference.

Study day 1 will consist of:
1. Further explanation and consent
Suitable patients to approach will be identified by the surgical team. The study will be described to them and a PIL left with them so that they can read it over at least 24 hours. On the day of the proposed study, the researchers will go over the PIL and answer any questions the participant may have. If they would like to volunteer for the research study and are a suitable candidate then the researchers will ask them to sign a consent form. Only then will they start the study.
2. Disease-appropriate rating scale assessments made and videoed for off-line review.
Patients with PD will be assessed using the Part III motor UPDRS, Unified dyskinesia rating scale and speech intelligibility test. The speech intelligibility test is the most widely used standardized test for measuring speech intelligibility and requires the patient to read 22 sentences, each of 5 to 15 words in length, for a total of 220 words. The intelligibility score is the percentage of words correctly understood by a native English speaker. Patients with essential tremor will be assessed using the tremor rating assessment scale (TETRAS) and the speech intelligibility test. Patients with dystonia will be assessed with the Burke Fahn Marsden dystonia rating scale (BFMDRS) and the speech intelligibility test. The performance of these rating scales and tests will also be videoed (with audio on) for off-line review (a necessary part of the speech intelligibility test).
3. Performance of the BRAIN test
This is an online keyboard tapping task used to assess upper limb motor function. This takes about two minutes to complete per arm and is tested bilaterally. It will be performed at the beginning of the study session and repeated during feedback-controlled stimulation. In some subjects we may substitute a manual joystick task for the BRAIN test, should it become important to assess particular components or phases of voluntary movements (the level of detail captured by the BRAIN test is less).
4. Attachment of recording devices
Pairs of electromyographic (EMG) recording electrodes will be taped over the skin overlying up to five muscles involved in tremor, rigidity or dystonic spasm. An accelerometer will be attached to the limb with the clinically most severe tremor or involuntary spasm (accelerometers are small devices, no bigger than a pen top, that are taped to a limb to pick up movement). These electrodes and devices will be connected to a CE marked TMSI amplifier (a recording device). The same amplifier will be connected to disposable leads coming from the deep brain stimulation electrodes.
5. Simultaneous recording of kinematic, EMG, scalp and depth EEG signals for 25 minutes
6. Trial stimulation to find the threshold for side-effects (usually tingling) over 10 minutes.
7. Rest while investigators select signals, or combination of signals, to be used in feedback-controlled stimulation of the basal ganglia and the optimal control policy. During this period stimulation will be set so that it is delivered at 130 Hz, with a pulse width of 90 microseconds in patients with PD or essential tremor and up to 200 microseconds in patients with dystonia, and a current that is just below the threshold for side-effects.
8. Trial of feedback-controlled stimulation during which recordings of kinematic, EMG, scalp and depth EEG signals are simultaneously made. During this disease-appropriate rating scale

assessments are made and videoed again, and the BRAIN test repeated.
9. If necessary, the patient rests while the investigators select alternative signals, or combination of signals, or control policy to be used in feedback-controlled stimulation of the basal ganglia.
10. Trial of feedback-controlled stimulation during which recordings of kinematic, EMG, scalp and depth EEG signals are simultaneously made. During this disease-appropriate rating scale assessments are made and videoed, and the BRAIN test repeated.

Study day 2 will only take place if the patient agrees and the steps assigned to stage 1 have not all been successfully completed. In this case, the researchers will use study day 2 to complete the steps defined above for study day 1. Day 2 would only complete the tests not done during day 1.

The set-up and testing will take up to 4 hours. No study day will last longer than this.

Intervention Type
Procedure/Surgery

Primary outcome(s)
Measured before and after feedback-controlled stimulation:
1. Kinematic recordings (accelerometer and BRAIN test in all patients) related to movement speed, spasms and the presence of tremor
2. Scores on standard, disease-specific clinical rating scales (UPDRS and UDysRS in Parkinson's disease, TETRAS in essential tremor and BFMRS and UDysRS in dystonia) and on Speech Intelligibility Test (all patients)
3. Scalp EEG (brain waves), depth EEG and EMG (muscle) recordings (all patients)

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

Completion date
09/07/2024

Eligibility

Key inclusion criteria
1. Participant is willing and able to give informed consent for participation in the study
2. Male or female, aged 18 to 80 years old
3. Diagnosed with Parkinson's disease, essential tremor or dystonia
4. Has completed stage 1 of a two-stage surgery for deep brain stimulation as therapy for their movement disorder

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Cognitive impairment (judged by the clinician taking consent as not having sufficient mental capacity to understand the study and its requirements). This is including anyone who, in the opinion of the clinician taking consent, is unlikely to retain sufficient mental capacity for the duration of their involvement in the study
2. Intracranial bleeding, cerebrospinal fluid leak or any other complication after the first stage of surgery

Date of first enrolment
10/01/2020

Date of final enrolment
09/01/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Oxford University Hospitals NHS Foundation Trust
John Radcliffe Hospital
Headley Way
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United Kingdom
OX3 9DU

Sponsor information

Organisation
University of Oxford

Funder(s)

Funder type
Government

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
National Institute for Health Research (NIHR) (UK)

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 and/or analysed during the current study during this study will be included in the subsequent results publication

IPD sharing plan summary
Other