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Understanding the sources of tremor variability in patients with essential tremor, Parkinson's, and dystonia – a non-invasive study of movement and brain signals

Submission date
14/01/2020

Recruitment status
No longer recruiting

Registration date
16/01/2020

Overall study status
Completed

Last Edited
05/12/2024

Condition category
Nervous System Diseases

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

Plain English summary of protocol

Background and study aims
This study aims to extend the current understanding of the relationship between oscillatory neural (nerve) activity in the peripheral and central nervous systems and the expression of motor deficits in movement disorders. The researchers will make recordings of patients making naturalistic movements to acquire signals generated by the muscles and brain. Specifically, they will use a new non-invasive neuroimaging system. This portable system uses sensors operating at room temperature (optically pumped magnetometers [OPM]) that can be worn on the participant's head using a closely fitting "head cast" moulded to the participant's MRI. Conventional recording systems (such as cryogenic magnetoencephalography or electroencephalography [EEG]) are highly susceptible to movement artefact which prevents the recording of brain activity during movement and makes the study of movement disorders difficult.
The use of portable OPM technology will allow the researchers to record patients moving in ways that correspond to their everyday activity. By obtaining high-quality neural recordings of structures thought to be associated with movement disorders the researchers can a) infer patterns of activity induced by a motor task designed to mimic daily motor activities; and b) ask how voluntary movement may interact with symptoms of movement disorders such as the expression of tremor.

Who can participate?
Patients aged 25 – 80 years with essential tremor, tremor-dominant or non-tremor dominant Parkinson's disease, or dystonic tremor

What does the study involve?
Patients perform a motor task capable of modulating motor deficits (e.g. intentional tremor, rest tremor, slowness of movement, and rigidity). Using these recordings the researchers hope to determine how the activity associated with voluntary movement acts to interact with the networks responsible for motor impairment. In the case of tremor dominant disorders, some

patients receive botulinum injections as part of their routine clinical care and perform the experiment twice, before and after this intervention.

What are the possible benefits and risks of participating?
There are no direct benefits to participants. Results from the study may however help in understanding the basic science of the diseases in question, as well as to develop future technologies and treatments. Risk to participants is minimal. All recordings are non-invasive and the study makes no intervention in the patient's care.

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

When is the study starting and how long is it expected to run for?
February 2019 to March 2025

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
1. Dr Timothy West
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2. Dr Hayriye Cagnan
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Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
254212

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Nil known

Study information

Scientific Title
The use of portable magnetoencephalography (MEG) in movement disorders

Acronym
pMEGMD

Study objectives
The central goal of this study is to better characterize the brain networks and associated oscillatory dynamics involved in the expression of motor deficits that accompany movement disorders and in particular tremor. Previous research has shown that measurements of neural activity in the deep brain structure of the thalamus, present oscillatory activity with frequencies that match those of peripheral measurements in the tremulous limbs of patients. Moreover, within the thalamus some regions present a coherent behaviour with specific muscles involved in tremor. Nevertheless, tremor seems to be a complex symptoms that emerges from the dysfunction of more than just one region (the thalamus and large part of the brain that it is connected to). The aim of this study is to simultaneous record activity from the different substrates of the tremor network (cerebellum, thalamus, sensorimotor and supplementary motor cortex) with OPMs and record the peripheral oscillatory properties of the tremulous limbs with accelerometers/motion capture. The OPM technology will allow the researchers to record brain activity during movement which is currently not possible with conventional recording

techniques such as EEG. In this way the aim is to explore for the first time the oscillatory interactions among structures of the tremor network and correlate these with the peripheral measurements of tremor.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 26/06/2020, Wales REC 5 (Castlebridge 4, 15-19 Cowbridge Rd E, Cardiff, CF11 9AB, United Kingdom; +44 7970422139; Wales.REC5@Wales.nhs.uk), ref: 20\WA\0124

Study design
Observational cross sectional study

Primary study design
Observational

Secondary study design
Cross sectional study

Study setting(s)
Other

Study type(s)
Other

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
Essential tremor; Parkinson's disease; dystonia

Interventions
RECRUITMENT
Patients suitable for this study will be identified by the clinical team who follow the clinical care of the patients. The invitation letter and PIS will be provided by the clinical team on behalf of the researchers. If patients are interested, they would then be asked to contact the researchers. There will be no additional risk to any patient who will take part in this study and there will not be any change to the medical care patients will receive regardless of whether the patient chooses to participate in the study or not. The proposed project will not offer benefit at an individual level to the participants. However, in due course, understanding the relationship between voluntary movement, neural activity and patients' symptoms would be invaluable in shaping our understanding of pathophysiology and has the potential to be implemented in the future as therapy. Please note a separate cohort of healthy, age-matched controls are also recruited for this study authorised by a healthy ethics approval at UCL.

PROCEDURE
Following recruitment, all participants will be invited to take part in the neuroimaging experiments. All experiments will be done at the UCL Wellcome Centre for Human Neuroimaging (WCHN), Queens Square.

MRI
Prior to any MEG recording the patient may have to undergo an anatomical MRI scan on a separate visit (several weeks before the actual experiment) so that a bespoke scanner cast (which would house the MEG sensors) can be made to fit the patients head shape. The MRI session will last one hour and consist of three 10-15 minute scanning
runs, and for ease of the patient, the researchers will try and co-ordinate this with their routine outpatient clinic appointment.

HEAD CAST
The structural MRI will be used by a contractor to design and manufacture a personalised head cast for each subject. MRI data is anonymized before transfer and deleted by the contractor upon delivery of the headcast to the WCHN. OPM-MEG Beside the MRI scan, in second session patients will be scanned using OPM's-MEG an accelerometer over the tremulous hand; and a motion capture system when conducting the motor-task. The researchers will also record the patients' muscle activity using surface EMG which are attached via adhesive electrodes to the skin. After setting up the recording equipment (around 20 minutes) and explaining the experiment to the patient, the patient will be asked to sit straight in a chair, with both hands resting in their laps.

Portable MEG
The new MEG technology (OPM) has been trialled in healthy subjects and is currently being trialed for the first time in patients with epilepsy. The new OPM sensors will be housed within the custom-built head-cast (built from the details obtained from the structural MRI). The exterior of the sensors becomes warm to the touch and has a maximum operating temperature rating that is far below that capable of causing harm to the patient (~41C). The participants will be warned that there is a possibility that this heating may give rise to temporary discomfort for a short period post-scanning. All subjects will be given the opportunity to wear/fit the scanner-casts prior to any scanning commencing. They will be informed that they can withdraw from the study at any time.

TASK
Recordings will be acquired from a group of ET, DT, and PD patients while performing a cued reaching task from rest. There will three tasks for the patient to complete, plus a resting recording session. The three tasks are a) reaching and pointing task; b) spiral tracing task; and c) a coin slot/peg and slot task mimicking standard clinical tests.
Considering the time spent at patient's set up plus the three tasks with a break in between, the entire experiment is expected to last 2 hours. A subset of patients receiving botulinum as part of their routine clinical care for essential tremor will be asked to return to the research site to repeat the experiment before/after they have received treatment.

ANALYSIS
The OPM's-MEG data will then be analysed offline after the study has occurred, using a combination of analysis software such as SPM, software developed at the WCHN, and Matlab. This will be performed by the applicant and a research MEG team with significant expertise in this field (Professor Gareth Barnes, Professor Vladimir Litvak, MEG
laboratory, UCL). All analysis will be done between Nuffield Department of Clinical Neuroscience (NDCN) at the University of Oxford; and the WCHN at UCL.

DATA TRANSFER
Data will be anonymized by recording data with a random identifier of which the key will be held by the CI. Data will be transferred for analysis between UCL and Oxford research sites, using an

encrypted hard drive. Dissemination of the data to the scientific community will be via publication in scientific journals and conference
presentations or publication of anonymized data to open accessible repository. Communication of results to patient groups will be via charities such as Parkinson's UK with whom the department has strong links. This project is not expected to generate any intellectual property.

Intervention Type
Other

Primary outcome measure
Regions involved in tremor-related networks imaged with great resolution using portable magnetoencephalography (MEG) during a set of motor tasks inducing tremor amplification and tremor suppression. Key data features include oscillatory power changes associated with different disease states. Measured at a single study visit.

Secondary outcome measures
Dynamic oscillatory profile of the non-tremor dominant PD network during movement, measured using using portable magnetoencephalography (MEG) at a single study visit

Overall study start date
01/02/2019

Completion date
01/03/2025

Eligibility

Key inclusion criteria
1. Patients with Essential Tremor without DBS implants for standard clinical indications
2. Patients with Parkinson's disease and tremor dominant without DBS implants for standard clinical indications
3. Patients with Parkinson's disease and non-tremor dominant without DBS implants for standard clinical indications
4. Patients with Dystonic tremor without DBS implants for standard clinical indications
5. Patients between 25 - 80 years of age
6. Patients have the capacity to give informed consent
7. Patients are MRI safe - i.e. no metal implants, history of working in metal industry etc

Participant type(s)
Patient

Age group
Adult

Lower age limit
25 Years

Upper age limit
80 Years

Sex
Both

Target number of participants
Maximum of 25 recruits per patient group: 25 – Tremor Dominant Parkinson's Disease (PD), 25 – Non-Tremor Dominant Parkinson's Disease, 25 – Essential Tremor (ET), 25 – Dystonic Tremor (DT), for a total of a maximum of 75 - 100 patients.

Total final enrolment
4

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. Pregnancy
3. Severe claustrophobia
4. Head or neck muscle weakness/fatigue
5. Severe visual impairment

Date of first enrolment
01/03/2020

Date of final enrolment
01/03/2023

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University of Oxford
Nuffield Department of Clinical Neurosciences
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Sponsor information

Organisation
University of Oxford

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Sponsor type
University/education

Website
http://www.ox.ac.uk/

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

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

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The patient information sheet (PIS), study protocol, and consent forms are all available upon reasonable request from the study CI. Results from this publication will be disseminated through a range of peer-reviewed scientific articles, conference presentations, and online articles.

Intention to publish date
01/03/2025

Individual participant data (IPD) sharing plan
Interested parties should contact the study CI Dr H Cagnan (hayriye.cagnan@ndcn.ox.ac.uk) for reasonable request of study data. The exact form and timeline for data sharing have not been decided at this time. Data will always be de-identified. Explicit consent for future data sharing is sought in question 8 of the consent form, and information on data sharing given in the PIS.

IPD sharing plan summary
Available on request